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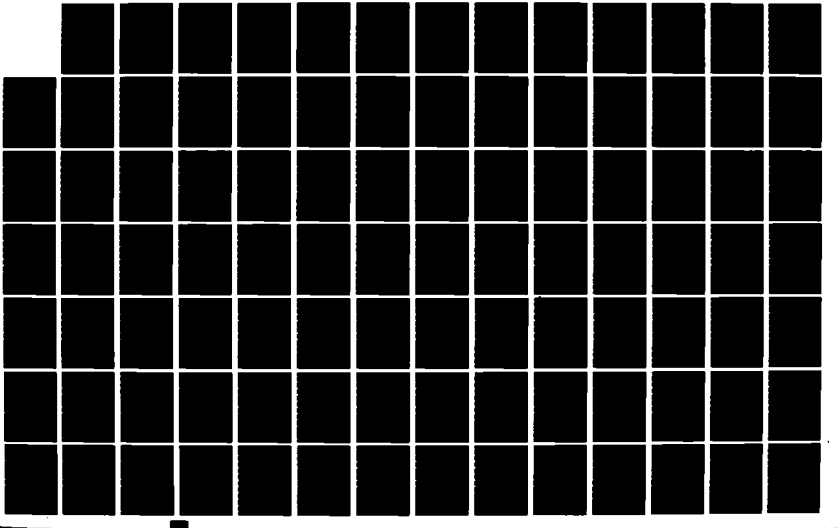

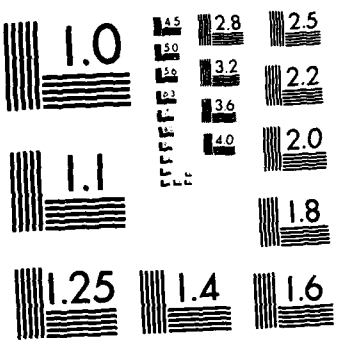

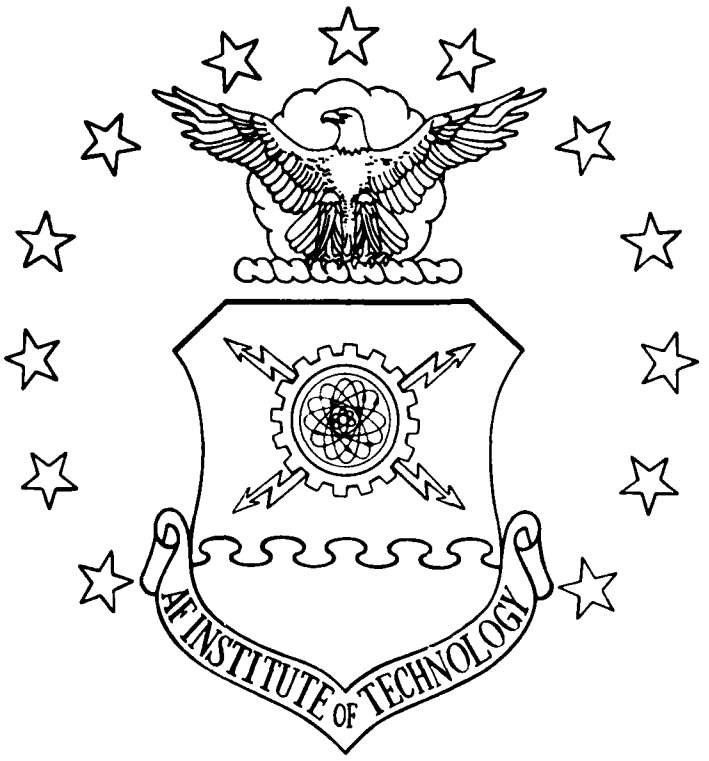

DEPARTMENT OF THE AIR FORCE

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Wright-Patterson Air Force Base, Ohio

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THE SIMULATION AND ANALYSIS OF AN EVOLUTIONARY MODEL OF DEOXYRIBONUCLEIC ACID(DNA)

Captain Richard E. McNally, USAF

LSSR 87-80

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A Monte Carlo simulation model was developed in order to evaluate model predictions with expectations of the evolutionary hypothesis of nearly neutral point mutations. The beta chain of hemoglobin was chosen as the strand of deoxyribonucleic acid(DNA) to be analyzed due to the extensive characterization of point mutations along the 146 amino acids of the protein chain. The nucleotide sequences of human, rabbit and a hypothetical ancestral hemoglobin were used as a starting point in the simulation. Three models of point mutations were tested. Equiprobable mutation from one nucleotide to any of the remaining three nucleotides composing DNA was one model. The second model incorporated observed first order probability of transition from each nucleotide to the remaining three nucleotides composing DNA using observed probabilities from three independent assessments. The third model was an Ising type model employing a probability of nucleotide change based on the nucleotide composition of the nearest neighbors. Use of these models resulted in evidence to suggest that five methods of simulating the mutations in an evolutionary system produced results that primarily differed in the way in which nucleotide changes resulted in a pattern of amino acid changes.

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THE SIMULATION AND ANALYSIS OF AN EVOLUTIONARY MODEL OF DEOXYRIBONUCLEIC ACID(DNA)

A Thesis

Presented to the Faculty of the School of Systems and Logistics

of the Air Force Institute of Technology

Air University

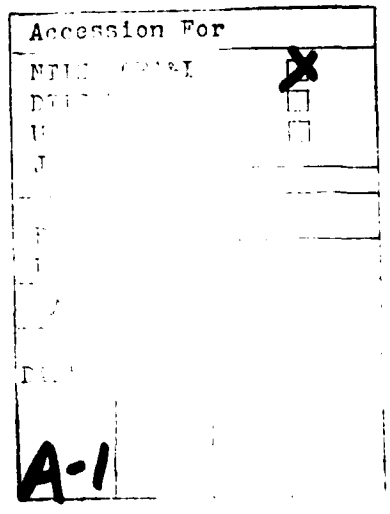
In Partial Fulfillment of the Requirements for the

Degree of Master of Science in Systems Management

By

Richard E. McNally, BS
Captain, USAF

September 1983



This thesis, written by

Captain Richard E. McNally

has been accepted by the undersigned on behalf of the faculty of the School of Systems and Logistics in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN SYSTEMS MANAGEMENT

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Thanks are due to all my advisors for their patience. Further, my coworkers and supervisors for indulging my behavior after many a long night on the computer deserve special mention.

My wife and children, for enduring the unending burden of the simulation and writing the thesis deserve far more recognition than these few words here. Without their love and help I would not have finished this work.

Richard E. McNally

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CHAPTER I

INTRODUCTION

Current evidence shows that deoxyribonucleic acid(DNA) is the carrier of genetic information within the nucleus of the cell. In protein synthesis, the DNA is transcribed into a complementary chain of messenger ribonucleic acid(mRNA). The mRNA chain is "read" in the cytoplasm. The reading process involves the incorporation of either an amino acid or the termination of the amino acid chain, depending on the specific three nucleotide sequence of the mRNA chain.

The genetic code which translates the nucleotide triplet into a specific amino acid (or a chain termination signal) has been found to be universal across all species of life so far studied (Epstein, 1966)(Melchar, 1970). The implication is that all forms of life have evolved after the genetic code became fixed in its present form some time in the distant past (Conrad, 1970)(Fox, 1974)(Hartman, 1975)(Jukes, 1973)(Orgel, 1972). The theoretical problem of the origin of life as known on this planet can then be divided into two component parts. First, the problem is to understand the chemistry and exobiology responsible for the development of protocells and the fixation of the genetic code represented by the universality of the genetic code

(Chernavskii, 1975)(Keosian, 1974)(Lacey, 1975)(Mazin, 1975)(Mikelsaar, 1975). The second problem is to understand the mechanisms at work after the fixation of the genetic code. Within this second area fall the mechanisms responsible for the range and diversity of life as observed today (Conrad, 1970)(Geracitano, 1971). The range and diversity is represented by the great number and complexity of species as well as the vast amount of difference observed within each species (Crow, 1970)(Geracitano, 1971)

The evolutionary theories of Darwin and the genetic systems of Mendel have been instrumental in providing a framework for categorizing and understanding many of the processes that have occured since the fixation of the code. The theories of Darwin and Mendel formed a school of thought which examined phenotype to form generalizations about genotype. This methodology has been continued by the modern population biologists (Jungck, 1971)(Lewontin, 1966)(Ohto, 1971). The main focus is on changes in population statistics as observed and applied using neo-Darwinian theories which emphasize selective advantage, or disadvantage (Epstein, 1967)(Kimura, 1969)(Papentin, 1973)(Richmond, 1970).

After the identification and characterization of the genetic code, many researchers began to look at the phenominon of evolution from the genotypic level (as represented by amino acid sequence within protein) towards

the phenotypic level. The redundant nature of the genetic code along with known characteristics of DNA enabled certain statistical projections about amino acid sequence and nucleotide sequence to be made. Random point mutations of the DNA chain could yield statistical evidence for changes in the amino acid structure of protein over a time period long enough to reflect evolutionary processes. Such projections lead to surprisingly accurate correlation between predicted time of seperation of species and archaeological data (Acher, 1974)(Clarke, 1970). Amino acid differences within species (known as polymorphic proteins) could be partially explained by random point mutations of neutral selection value (Kimura, 1971)(Sueoka, 1961)(Zuckerkandl, 1972).

The overall objective of this thesis will be to provide a framework to examine the random mutation hypothesis. From this framework a better understanding of the possibilities and limitations imposed by random mutation can be evaluated. Implications about the evolutionary potential of the information carrying system and the present equilibrium of that system may be possible.

This thesis is written in five chapters. This, the first chapter, has presented a brief introduction to several of the ideas of current interest in evolutionary biology. This section identifies the organization of the remainder of the paper. The second chapter reports the relevant

information gathered during the course of the research into the evolutionary potential of bio-organic information transmitting compounds, the characteristics of mutations occurring within the system, and information on hemoglobin's evolutionary and mutational behavior. The third chapter addresses the methodology to be employed in this thesis. This includes the development of a modeling approach to the point mutation of the DNA sequence responsible for producing viable beta hemoglobin chains as well as the techniques used to evaluate the model's performance and the results on hypothesis testing. The fourth chapter lists the results of analysis I performed on the simulation results obtained. The fifth chapter reflects the conclusions that I have been able to gather from the modeling and analysis results obtained to date.

CHAPTER II

BACKGROUND

The first section will be a quick tutorial of different portions of the information transmission system of cells. This will consist of brief outlines of the compounds and simplified descriptions of the functioning of the system. This section will also include a review of genetic mutations. The second section will contain a bibliographic review of the concept of evolutionary forces at work in the mutation of DNA. Different theories as to the operate mechanism will be discussed as well as some of the implications of these theories.

The chromosomes of organisms are composed of nucleoproteins. Proteins such as histones and nucleic acids comprise the nucleoproteins. The nucleic acids have been associated with the transmission of genetic information while the histones play a role in the stabilization of the compounds and mechanisms involved(Stansfield, 1969)(Stryer, 1975).

Deoxyribonucleic acid is the repository of genetic information in all eukaryotes. DNA is stabilized into chains thousands of nucleotides long that form a double stranded helix. The backbone of each chain consists of five

carbon sugar compounds oxygenated at the 2' position linked by phospate to form 5'=>3' phosphodiester linkages. The helix is held together by the interaction of the bases attached to the 1' carbon of the sugar. The paired organic bases found in DNA are the purines adenine(A) and guanine(G) and the pyrimidines thymine(T) and cytosine(C). In normal DNA with unmodified bases, cytosine always pairs with three hydrogen bonds with guanine while adenine always pairs with two hydrogen bonds with thymine. The nucleotide unit consists of the sugar, the phosphate, and the base(Stansfield, 1969)(Stryer, 1975).

Ribonucleic acid(RNA) is another class of nucleic acid. RNA differs from DNA in that the base sugar, again a pentose, does not have an oxygen at the 2' position. RNA is thought of as primarily a single stranded nucleotide, however, the ability of RNA to stabilize itself by forming double and even four stranded chains is thought to play a key role in several of the mechanisms and the results of several thermodynamic considerations. RNA constains the pyrimidine uracil(U) instead of thymine within its structure. RNA is typically much shorter than DNA and is found both within and outside of the cell nucleus(Stansfield, 1969),(Stryer, 1975).

RNA plays a predominate role in protein synthesis. There are three common types of RNA designated as mRNA, tRNA, and rRNA. Messenger RNA, or mRNA, is transcribed from

DNA within the nucleus of the cell and is brought to the cytoplasm. Transfer RNA, or tRNA, is found in the cytoplasm and is active in selectively positioning the appropriate amino acid into the growing protein chain based on the codon of the mRNA carrying the template for protein synthesis. Ribosomal RNA, or rRNA, is actually a class of different molecular weight components with protein components which serve as the binding site for mRNA and tRNA in the translation process(Stansfield, 1969)(Stryer, 1975).

The individual hydrogen bonds linking the bases of the DNA chains are not strong compared to typical covalent chemical bonds such as those that connect the sugar to the phosphate or to the base, however, the large number of bonds form a very powerful and a very stable chain. DNA is replicated with the assistance of enzymes known as DNA-polymerases which assist in the separation of the DNA helix. The two single DNA strands each form a new double stranded DNA helix by the addition of nucleotides in a new second DNA strand which forms in the 5'=>3' direction. The replication of DNA occurs extremely fast. As a practical consideration, single stranded DNA is very rarely found(Stansfield, 1969)(Stryer, 1975).

The nucleotide sequence of DNA is the blueprint for protein synthesis. Proteins form the major structural components of the cell as well as the enzymes necessary to catalyze the biological reactions which are essential for

life as we know it. Proteins are composed of a large number of amino acid residues which forms the primary structure. Proteins form stable secondary and tertiary structures based on the thermodynamic equillibrium of the chain in the ionic environment in which it exists. While the primary structure of the protein may be responsible for the production of an active site in an enzyme, it is the secondary structure which is reflected within the environment which ultimately determines the catalytic ability of the protein. If the ionic or temperature conditions cause the secondary structure to change, the catalytic ability of the enzyme is usually lost. Proteins are comprised of 20 different amino acids as reflected in table 2.1(Stansfield, 1969)(Stryer, 1975).

Table 2.1
Amino Acids By Decreasing Frequency of Occurance

1	G	Gly	Glycine	11	I	Ile	Ileucine
2	A	Ala	Alanine	12	R	Arg	Arginine
3	L	Leu	Leucine	13	N	Asn	Asparagine
4	S	Ser	Serine	14	Q	Gln	Glutamine
5	V	Val	Valine	15	F	Phe	Phenylalanine
6	K	Lys	Lysine	16	Y	Tyr	Tyrosine
7	T	Thr	Threonine	17	C	Cys	Cysteine
8	E	Glu	Glutamic Acid	18	H	His	Histidine
9	P	Pro	Proline	19	M	Met	Methionine
10	D	Asp	Aspartic Acid	20	W	Trp	Tryptophan

The mRNA is translated by tRNA while being bound by rRNA to form proteins. Each amino acid has an amino group at one end and a carboxyl group at the other. Proteins are

synthesized by the addition of new amino acids at the carboxyl terminal of the growing protein chain based on the "reading" of the mRNA in the 5'=>3' direction. The "reading" of the RNA message is conducted in accordance with the genetic code. The genetic code is a catalog of sixty-four three base codons which form a degenerate reference set for the twenty available amino acids from the four

Table 2.2
Genetic Code

5' DNA 3'	5' RNA 3'	Amino Acid	5' DNA 3'	5' RNA 3'	Amino Acid
AAA	UUU	Phe	GAA	UUC	Phe
TAA	UUA	Leu	CAA	UUG	Leu
AGA	UCU	Ser	GGA	UCC	Ser
TGA	UCA	Ser	CGA	UCG	Ser
ATA	UAU	Tyr	GTA	UAC	Tyr
TTA	UAA	Stop	CTA	UAG	Stop
ACA	UGU	Cys	GCA	UGC	Cys
TCA	UGA	Stop	CCA	UGG	Trp
AAG	CUU	Leu	GAG	CUC	Leu
TAG	CUA	Leu	CAG	CUG	Leu
AGG	CCU	Pro	GGG	CCC	Pro
TGG	CCA	Pro	CGG	CCG	Pro
ATG	CAU	His	GTG	CAC	His
TTG	CAA	Gln	CTG	CAG	Gln
ACG	CGU	Arg	GCG	CGC	Arg
TCG	CCG	Arg	CCG	CGG	Arg
AAT	AUU	Ile	GAT	AUC	Ile
TAT	AUA	Ile	CAT	AUG	Met
AGT	ACU	Thr	GGT	ACC	Thr
TGT	ACA	Thr	CGT	ACG	Thr
ATT	AAU	Asn	GTT	AAC	Asn
TTT	AAA	Lys	CTT	AAG	Lys
ACT	AGU	Ser	GCT	AGC	Ser
TCT	AGA	Arg	CCT	AGG	Arg
AAC	GUU	Val	GAC	GUC	Val
TAC	GUA	Val	CAC	GUG	Val
AGC	GCU	Ala	GGC	GCC	Ala
TGC	GCA	Ala	CGC	GCG	Ala
ATC	GAU	Asp	GTC	GAC	Asp
TTC	GAA	Glu	CTC	GAG	Gly
ACC	GGU	Gly	GCC	GGC	Gly
TCC	GGA	Gly	CCC	GGG	Gly

nucleotide bases available. The code can be seen in Table 2.2.

The attachment of an amino acid to its tRNA is mediated by specific enzymes in a process called activation. The tRNA sequence contains a three nucleotide anticodon which is complementary to the mRNA codon. The tRNA is positioned at the translation site where the rRNA is "reading" mRNA in the 5'=>3' direction. The amino group of the tRNA bound amino acid is brought into a proximal position to the carboxyl group of the growing peptide chain. Enzymes are active in the formation of the peptide bond formed at this site which joins the the amino acid to the protein. The tRNA is released from both its amino acid and the mRNA chain. When the ribosome meets the end of the mRNA or encounters an in-phase termination codon, the protein's primary structure, consisting of the sequence of amino acids is complete. The secondary structure, or the three dimensional structure of the protein, is probably also complete at this point or shortly after release from the ribosome. The secondary structure is created by the formation of three dimensional structures such as the alpha-helix or beta-pleat sheet. Quarternary structures that stabilize the hydrophobic and hydrophillic regions of the protein as well as the formation of internal covalent bonds (such as between cysteine residues). The tertiary structure of multiple proteins may form a quaternary structure. For instance, two alpha and

two beta hemoglobin chains combine to form the functional complex. Any alteration of the final configuration may inactivate the protein(Stansfield, 1969)(Stryer, 1975).

Each tRNA consists of 75 to 80 nucleotides in a specific order. The 3' end of all tRNA's contain the sequence CCA. The 5' end terminates in a guanine residue. Pseudouradilic acid, inosinic acid, and a few other modified bases are found in tRNAs. The tRNAs have a characteristic three dimensional four arm stucture with helical sections and single stranded loops. One of the unpaired loops contains the anticodon(Stansfield, 1969)(Stryer, 1975).

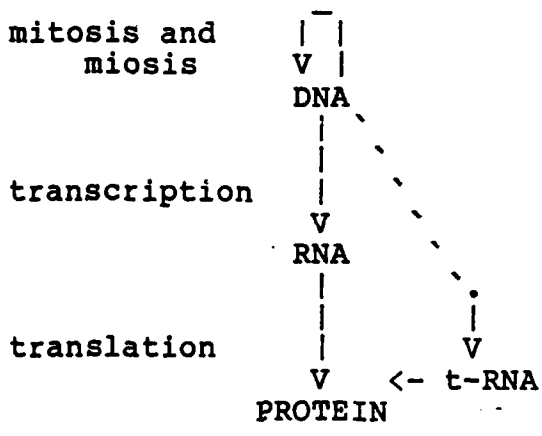

Figure 2.1
Simplified Schematic Of Protein Synthesis

More than 30 different proteins have been associated with rRNA in ribosomes. Three sites conceptually exist on functional ribosomes. A decoding site binds the activated tRNA to the mRNA codon. A condensing site joins the amino

acid to the growing polypeptide chain. An exit site at which the tRNA becomes separated from the protein, mRNA, and ribosome. The tRNA is processed in turn thru all three sites of the ribosome(Stansfield, 1969)(Stryer, 1975).

Most genes are relatively stable and mutation is a very rare event. The average mutation rate has been estimated at one accepted point mutation occurring in million genes. Other genes have mutation rates estimated at one mutation per occurring in ten genes. Mutation at the genotypic level can only be examined directly very recently. Present estimates are directly tied to observations of the proteins produced. When the proteins that are produced cause differences observable in the organism's behavior, a mutation could be identified which caused the change(Stansfield, 1969)(Stryer, 1975).

The majority of mutations are lethal to the organism and result in the death of the organism. The mutant gene, even in the case of lethal effects, are kept at a low frequency with in the population. The effects on the target population and the frequency of the allele can be predicted by modeling techniques used in population genetics. Population genetics have been used to study the transfer of advantagious and neutral alleles within a population. Mutant types produce organism which compete within the ecosystem. Natural selection appears to play an important role in the level of an allele in a population. To date,

all of the population genetic studies that have been conducted rely on phenotypic manifestions. Any genotypic change that occurs in the proteins of an organism can only be evaluated using present techniques when the genotypic change causes a phenotypic change. The hiearchy of information transmission is presented in figure 2.2(Stansfield, 1969)(Stryer, 1975).

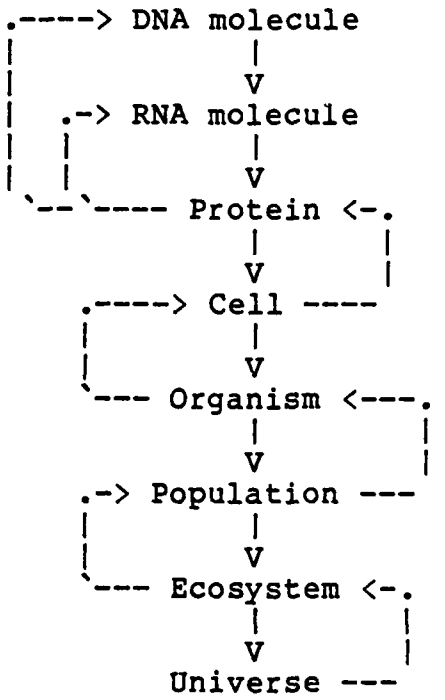

Figure 2.2
Hieracrhy Of Biological Information Transfer

There a several types of mutations possible. Each type may be identified by several different sets of terminology which can be used to describe non-exclusive mutation events. When discussing the size of a mutation, the two classifications most used are point and gross. Point

mutations are usually associated with changes at a single nucleotide pair. Gross mutations involve large areas of genetic information. This could describe mutations to multiple nucleotides, an entire gene, or even entire chromosomes(Stansfield, 1969)(Stryer, 1975).

Mutations can also be classified as to quality. Structural mutations affect the nucleotide content of the gene. Substitution mutations, deletion mutations, and insertion mutations, and insertion mutations belong in this category. Transition mutations occur when one purine nucleotide is substituted for another purine or when one pyrimidine is substituted for another pyrimidine. Deletion mutations occur when some part of the gene is lost from the gene. Insertion mutations occur when nucleotides are added to the gene(Stansfield, 1969).

The origin of the mutation is also a source of classification. A mutation is called spontaneous when the origin is unknown. This is the category where the random mutations thought to be important in evolutionary drift. Genetic control mutations are thought to occur when the influence of a specific gene affects one or many other genes. Induced mutations occur when ionizing, noionizing radiation, and chemical mutagens which are not normally included in the environment affects the gene(Stansfield, 1969).

The magnitude of the phenotypic effect is also a

classification scheme for mutation. Some alleles can be distinguished by the frequency with which they mutate. Isoalleles which produce seemingly identical pheotypes when in homozygous or heterozygous combinations, but in combination with other alleles are identifiable. Mutants which affect the viability or the reproductive vigor of the organism can be identified(Stansfield, 1969).

Mutations can be identified by the direction of the phenotypic response. A mutation is considered forward when the normal phenotypic characteristic suddenly becomes an abnormal phenotype. A back mutation is the return to normal phenotype after an abnormal phenotype was observed. Back mutations have been observed to occur either by a change at the initial location within the gene or at a remote site in a different gene(Stansfield, 1969).

Mutations can also be cataloged as to the type of cell. A somatic mutation occurs in the non-reproductive cells of the body. This phenominon is seen when only a part of the organism demonstrates the effect of the mutation. Gametic mutation occurs in the reproductive cells of the organism and produces an heritable change seen in the following generations of the organism(Stansfield, 1969).

To systematically understand the relationships involved in the mutation of an organisms DNA, it is important to understand the control relationships that exist. Figure 2.3 examplifies this type of approach.

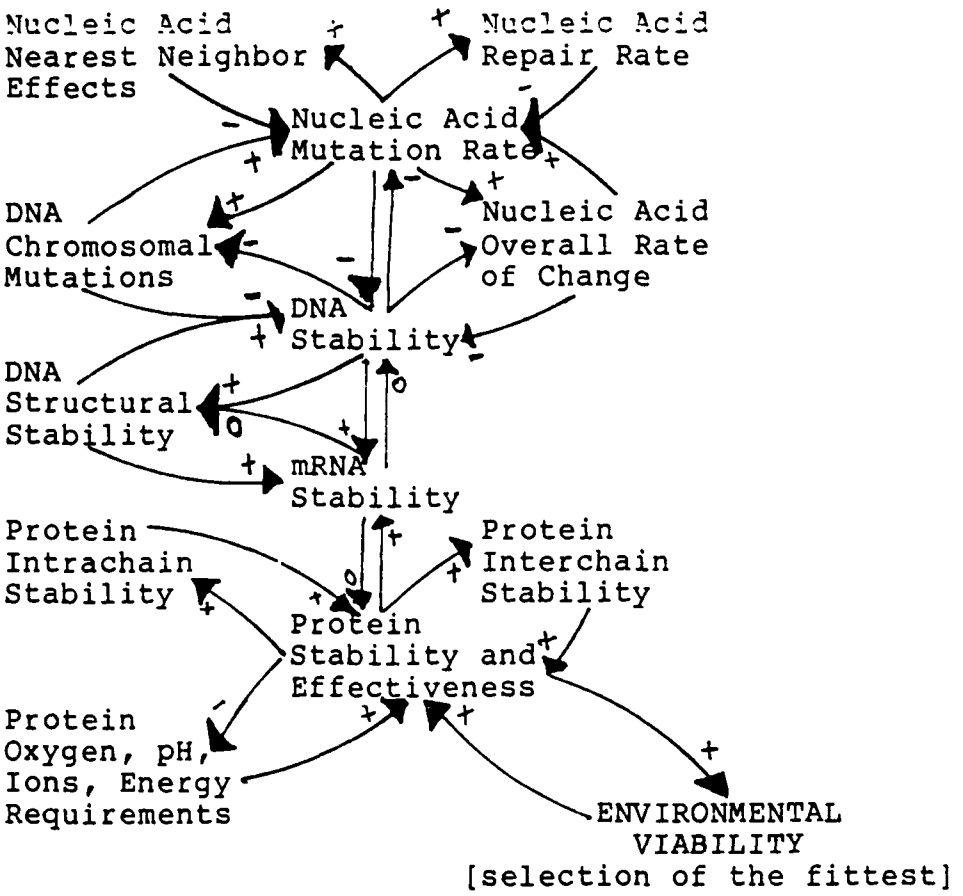

Figure 2.3
Functional Environmental Relationships

In the 1960's it was established that proteins reflected the genotypic content of the gene. This reflection was found to be common across all forms of life according to the genetic code. The amino acid sequence was the result of a specific and ordered sequence of nucleotides in DNA. It is clear that these proteins represent the end products of molecular evolution. The study of amino acid sequences has enabled a new perspective on the study of evolution. These sequences represent a more detailed view

of the phenotype of the organism than is possible from even the most detailed observation of the characteristics of the organism. Atlas of Protein Sequence and Sturcture edited by Dayhoff and published in 1972 provided a great deal of information on the amino acid sequences of many different proteins and many different species. Because a large qunatity of purified protein and the massive labor efforts involved in doing amino acid sequences, the amount of information which can be found is still pretty sparse. Cytochrome C and hemoglobin are the two proteins which have received the most attention. Sequences from many species have been collected for these two proteins.

The second generation of data on information macromolecules has already begun. New techniques for the rapid and automatic sequencing of very small quantities of nucleic acid are now available. Sequencing of mRNA for the hemoglobin chains is now available for use in this study. The sequencing of tRNA have been completed. Using the information from the structure of informational molecules is better than using either observable characteristics or even amino acid sequencing. Proteins reflect the informational structure of the gene far better than any observable characteristic of the organism. The chemistry of the cell is the result in large measure to the functional capability of the available proteins. Amino acid sequences directly reflect the content of the DNA. A single nucleotide change

can result in the placement of a new amino acid into a protein. This amino acid replacement may or may not affect any observable characteristic of the protein. A single amino acid replacement in hemoglobin causes sickle cell anemia. However, since the genetic code is reduntant with some amino acids being coded by as many as 6 codons, many changes in nucleic acid result in no change to the primary protein structure. In fact, studies show that the structure of the genetic code is such that most of the changes in nucleotide content either produce the same, or a chemically related amino acid. Another factor to be considered is the existance of multiple genetic loci coding for the same protein. This can result in the production of multiple proteins with the same basic structure and function. The study of the nucleic acid sequence of functional proteins allows a more in-depth view of the phenominon at work at the genetic level while keeping the product tied to the functional structural requirements placed on the protein chain.

Use of a thorough understanding of the structure-function relationships of proteins together with information available from analysis can result in an understanding of the evolutionary mechanism that is far better than what is commonly known to date. Even the work using these techniques that have been accomplished using the amino acid sequence information has the increased difficulty associated

with the redundancy of the code. Understanding evolutionary mechanics at the level of the protein chain does not directly reflect the process at the level of nucleic acid. For instance, the colinearity of DNA and protein has been presumed for some time now. Most of the information was derived from the translation of mRNA into proteins. When the DNA sequence of the hemoglobin gene was identified, it was found to have a large region of non-coded intervening sequences. Also, recently the discovery of large portions of repeated sequences of DNA identified in mammalian DNA have spurred new questions. Study of the evolutionary impact of random mutation and the effect of processes occurring at the level of the nucleic acids must be conducted using relationships at that level. Using relationships at the amino acid level given the unique information transmission mechanism of the genetic code is likely to give a different perspective of reality.

From an evolutionary viewpoint, the primary structure of a protein is in large part the end point of a biological phenomenon. The secondary structure and binding to cofactors or in the case of hemoglobin, the binding of the heme, to produce a functionally proficient molecule within the cell is the direct result of the primary sequence. Any changes in the primary structure which alters the function of the protein will have very large consequences on the survivability of the cell, and the organism. On the

other hand, many changes at different parts of the protein result in little or no change in the capability of the protein to perform its biochemical function.

For hemoglobin, X-ray crystallographic determinations on the structure of hemoglobin chains from many species show nearly the same tertiary and quartinary structure. Biochemical differences in the oxygen transport capability of the molecule are very small. Since many of the amino acid positions have been observed to have different residues that result in changes that do not affect function, there has been considerable debate on the effect of neutral mutations and the role that random genetic drift may have on the evolutionary process. Changes that are not the result of some selective advantage appear to be occuring throughout the proteins of the cells. Even a protein with the survival requirements that are tied to the functional demands of hemoglobin appear to have a large number of residues that may be changed among several amino acids. Figure 3.2 reflects the variety of residues that a review of the literature suggests as possible. Of note at this time is the use of Figure 3.2. That these amino acids have been found in some of the beta chains of different species is not to say by any stretch of the imagination that all replacements are neutral. In fact, many of these changes have been associated with decreased function of the hemoglobin. Further, many of these residues are only

acceptable when other residues on the chain have already been substituted. Other changes are undoubtedly not acceptable on a survival basis when combined with other changes. Because of the limited nature of detailed functional and survival information on each individual possible change the simplifing assumtion made in this study was that all possible combinations would be allowed in this modeling effort.

CHAPTER III

METHODOLOGY

After completing the literature review, it was obvious that there exists strong evidence that point mutations in the amino acid sequences of several different proteins appear to have significant evolutionary patterns that can be studied. The two most commonly characterized, studied, and analyzed protein chains were cytochrome c and hemoglobin. Both consist of protein chains longer than 100 amino acids. Both have had extensive studies of polymorphic variants and of the secondary, and tertiary structures. Many investigators have sequenced both compounds from many different species. Recent work on sequencing the mRNA of the different hemoglobin chains in several species have enabled this study.

The target sequence of the DNA represention of the beta chain of hemoglobin was chosen. The unique availability of this information complemented the existing data on point mutations and amino acid differences among and between different species. Work by Dayhoff and by Fitch to construct hemoglobin ancestrial trees based on similarity studies of the amino acid differences between species and between different chains of hemoglobin provided insightful guidance.

For this study, two known mRNA sequences of beta hemoglobin were chosen, that of human and that of rabbit. A third sequence based on the amino acid sequence of an hypothetical ancestral beta hemoglobin chain which should be evolutionary common. Approximately equal numbers of point mutations were accepted into the human and the rabbit chains. The ancestral beta hemoglobin chain was characterized and included in the modeling effort. The ancestral beta hemoglobin I selected to use for this effort was identified as locus 28 in Dayhoff's Atlas of Protein Sequence and Structure.

Table 3.1 presents the DNA representation of the beta hemoglobin chain that were chosen for the present study. Very few point mutations exist in the data between the human and the rabbit DNA. Likewise, there are few point mutations between the ancestral(early) DNA and either the human or the rabbit DNA. In formulating the ancestral nucleotide string, minimizing the differences between existing nucleotides in the human and rabit DNA was a goal. The ancestral protein string had very few changes in amino acids. If the human and rabbit codon at any particular location was identical and if the ancestral amino acid was that same codon, then the ancestral amino acid was assumed to have the same codon as the other two DNA chains. If the human and rabbit codons were different, then the codon chosen to represent the ancestral codon was chosen to have the minimum number of

nucleotide differences with both chains and still code for the predicted amino acid. If both the human and the rabbit codons were equidistant, then the nearest neighbor nucleotide transition rate was used. The nucleotide chosen for the ancestral codon was that nucleotide that had the highest transition probability to the needed nucleotide. No equivalent probabilities were encountered.

Table 3.1
Beta Hemoglobin DNA

Amino Acid #	5'=>3' Man	Rabbit	Early	Amino Acid #	5'=>3' Man	Rabbit	Early	Amino Acid #	5'=>3' Man	Rabbit	Early
0	CAT	CAT	CAT	50	AGT	AGA	AGA	100	AGG	AGG	AGG
1	CAC	CAC	CAC	51	AGG	TGC	AGC	101	CTC	CTC	CTC
2	GTG	ATG	ATG	52	ATC	ATT	ATC	102	GTT	GTT	GTT
3	CAG	CAC	CAC	53	TGC	TGC	TGC	103	GAA	GAA	GAA
4	AGT	GGA	GGT	54	AAC	AAC	AAC	104	CCT	CCT	CTT
5	AGG	ACT	AGC	55	CAT	CAT	CAT	105	GAG	GAG	GAG
6	CTC	CTC	CTC	56	GCC	GTT	GCC	106	CAG	CAG	CAG
7	CTC	CTC	CTC	57	GTT	ATT	ATT	107	GCC	GCC	GCC
8	CTT	CTT	CTT	58	AGG	AGG	AGG	108	GTT	GTT	GTT
9	AGA	AGA	AGC	59	CTT	CTT	CTT	109	CAC	CAC	CAC
10	CGC	CGC	CGC	60	CAC	CAC	CAC	110	CAG	CAG	CAG
11	AAC	GAC	AAT	61	CTT	CTT	CTT	111	GAC	AAC	AAC
12	AGT	AGT	AGT	62	AGC	AGC	AGC	112	ACA	AAT	AAT
13	GGC	GGC	GGA	63	ATG	ATG	ATG	113	CAC	CAC	CAC
14	CAG	CAG	CAG	64	GCC	GCC	GCC	114	CAG	CAG	CAG
15	CCA	CAC	CAC	65	CTT	CTT	CTT	115	GGC	AGA	AGC
16	GCC	GCC	GCC	66	TTT	CTT	TTT	116	ATG	ATG	AGG
17	CTT	CTT	CTT	67	CAC	CAC	CAC	117	GTG	ATG	ATG
18	CAC	CAC	CAC	68	GAG	CAG	CAG	118	AAA	AAA	AAA
19	GTT	ATT	ATT	69	ACC	AGC	ACC	119	GCC	GCC	GCC
20	CAC	CAC	CAC	70	GGC	GGC	GGC	120	TTT	TTT	TTT
21	ATC	TTC	TTC	71	AAA	GAA	AAA	121	TTC	TTC	TTC
22	TTC	TTC	TTC	72	ACT	ACT	ACC	122	GAA	GAA	GAA
23	AAC	AAC	AAC	73	ATG	CTC	ATC	123	GGT	AGT	AGT
24	ACC	ACC	ACC	74	GCC	ACC	ACC	124	TGG	AGG	AGG
25	ACC	ACC	ACC	75	CAG	CAG	CAG	125	TGG	CTG	TTC
26	CTC	CTC	CTC	76	AGC	ACT	TTT	126	CAC	CAC	CAC
27	GGC	GGC	GGC	77	GTG	GTG	GTG	127	CTG	CTG	CTG
28	CAG	CAG	CAG	78	CAG	CAG	CAG	128	AGC	AGC	AGC
29	GCC	GCC	GCC	79	GTC	GTC	GTC	129	GGC	GGC	GGC
30	CAT	CCT	CAT	80	GTT	GTT	GTT	130	ATA	ATA	CCA
31	CAG	CAG	CAG	81	GAG	GAG	GAG	131	CTG	CTG	CTG

Table 3.1 Continued

Amino Acid #	5'=>3' Man	Rabbit	Early	Amino Acid #	5'=>3' Man	Rabbit	Early	Amino Acid #	5'=>3' Man	Rabbit	Early
32	CAG	CAG	CAG	82	CTT	TTT	TTT	132	TTT	CTT	TTT
33	CAC	AAC	AAC	83	GCC	GCC	GCC	133	CAC	CAC	CAC
34	GAC	GAC	GAC	84	GGT	GGT	GTT	134	CAC	CAC	CAC
35	GTA	GTA	GTA	85	AAA	AAA	AAA	135	AGC	AGC	AGC
36	AGG	TGG	AGG	86	GGC	AGC	AGC	136	ACC	ACC	ACC
37	CCA	CCA	CCA	87	TGT	CTT	TTT	137	CAC	CAC	CAC
38	GGT	GGT	GGT	88	CAG	CAG	CAG	138	AGC	GGC	AGC
39	CTG	CTG	CTG	89	ACT	ACT	ACT	139	ATT	ATT	ATT
40	CCT	CCT	CCT	90	CTC	TTC	TTC	140	GGC	GGC	GGC
41	GAA	GAA	GAA	91	CAG	CAG	CAG	141	CAG	CAG	CAG
42	AAA	GAA	AAA	92	GTG	GTG	GTG	142	GGC	AGC	AGC
43	CTC	CTC	GTC	93	ACA	ACA	ACA	143	GTG	GTG	GTG
44	GGA	GGA	GGA	94	GTC	GTC	GTC	144	CTT	TTT	TTT
45	AAA	AAA	AAA	95	CTT	CTT	CTT	145	ATA	GTA	ATA
46	CCC	CCC	CCC	96	CAG	CAG	CAG	146	GTG	GTG	GTG
47	ATC	GTC	ATC	97	GTG	GTG	GTG	147	TTA	TTA	TTA
48	CAG	CAG	CAG	98	CAC	CAC	CAC				
49	GGA	GGA	GGA	99	ATC	ATC	ATC(BARRALLE,1977A:1093)				

The model was set up so that all three DNA sequences were run with the same random number stream generating point mutations for each run of the model. The complete model can be found in Appendix A of this report.

Potential point mutations were assessed by comparison of the random number with the assigned probability of a mutation occurring. The probability of a mutation occurring at any nucleotide was dependent upon the structure of the model and the selection of the data coefficient chosen. Three structures were tested for creating point mutation. The first technique is called the random method. If the random number representing the probability of having a point mutation is below the threshold established for having

a mutation, then the mutation was tested for validity/reasonableness. Each nucleotide was assigned an equal probability of becoming changed to any of the other three nucleotides and this was the point mutation tested. Point mutation testing consisted of evaluating whether or not the amino acid that would result from the new codon was possible at that position. Possibility was arbitrarily estabilished in this effort as having the amino acid in question at that position recorded either as a known point mutation, or protein polymorph, or even an amino acid found in one of the other species for which beta hemoglobin protein sequenceing had been conducted. See Table 3.2 for a compiled list of acceptable amino acids at each position on the chain.

Table 3.2
Allowable Amino Acid by Position

Beta Hemoglobin Position	Amino Acid	Beta Hemoglobin Position	Amino Acid
1	T,V,M,P,G	74	G,A,D
2	H,L,Q,E,D,N,Y,R	75	L,V,M,I,T
3	L,K,F,W	76	A,N,S,T,H,K,G,Q,E
4	T,S,A	77	H,N,E,Q,D
5	P,D,S,G,E,A,K,N	78	L,P
6	E,A,D,G,K,Q,P,V,S	79	D,N,E
7	E,A,G,D,N,Q,K	80	N,D,K,S
8	K,D,S	81	L,I
9	S,A,N,T,V,D,C,H,G,E	82	K
10	A,T,H,L,E,Q,S	83	G,A,N
11	V,G,I	84	T,A,H
12	T,S,N,A,L,D,R,I,V,K	85	F,Y
13	A,G,T,S,C,N	86	A,S
14	L,S,F,R	87	T,S,K,E,A,Q,N,H
15	W,F,G,S	88	L,R,P
16	G,S,A,D,R	89	S,T

Table 3.2 Continued

Beta Hemoglobin Position	Amino Acid
17	K,I,E,H
18	V,K,I,H
19	N,K,H,G,E,Q,A,D
20	V,A,S,E,L,I,D,G,P
21	D,E,H,A,G,Q,N
22	E,D,K,A,N,Q,G
23	V,D,A,T,C,I,L
24	G,L,R,V
25	G,K,A,R
26	E,Q,Y,K
27	A,H,T
28	L,P
29	G,A
30	R,S
31	L
32	L
33	V,L,I
34	V
35	Y,F
36	P
37	W,S
38	T
39	E,R,Q,S
40	R
41	F,Y
42	F,S
43	E,S,D,Q,T,A,R
44	S,H,T,A,E,Q
45	F,L
46	G,E
47	D,A,N
48	L
49	S,G
50	T,S,N,D,K
51	P,A
52	D,N,S,H,G,K,E,A
53	A
54	V,I
55	M,L,C
56	G,N,S,D,A,H
57	N,D,A
58	P,A,R
59	K,E,T,M,Q
60	V
61	K,L,N,E,R
62	A,G
63	H,R,Y

Beta Hemoglobin Position	Amino Acid
90	E,Q,K
91	L,Y,P
92	H,Y
93	C,S
94	D,V,N
95	K,A,E,Q
96	L
97	H,E,R
98	V,M
99	D,N,H,Y
100	P
101	E,Q,A
102	N,K,T,D
103	F
104	R,K,N
105	L,R
106	L
107	G
108	N,D
109	V,M,S,I,A
110	L,I,F,V
111	V,D,N,A,I
112	C,L,I,S,V,T,H
113	V,C,E,A
114	L
115	A,G,S
116	H,D,N,R,I,E
117	H,N,R
118	F,L,H
119	G,Q,F,S,K,D
120	K,D,N,S,H,E
121	E,D,Q,N,E,Q,K
122	F
123	T,D,N,S
124	P,I,R
125	P,A,Q,R,E,V,L,G,D,C
126	V,A,L,M,T,E,C
127	Q,E,L
128	A,V,H,S
129	A,S,D,Q,E,G,N
130	Y,F,H,W,L,D
131	Q,E,L
132	K,A,Q,E
133	V,M,L,H
134	V,F
135	A,T,C,S,R
136	G,A,D,V

Table 3.2 Continued

Beta Hemoglobin Position	Amino Acid	Beta Hemoglobin Position	Amino Acid
64	G	137	V
65	K,S,A,E	138	A,G,S
66	K,E	139	N,A,D,T,S,H
67	V,A,D,E	140	A
68	L,I	141	L,R
69	P,R,G,T,A,S,D,N,H,V,E,Q	142	A,S,G
70	A,T,S	143	H,S,K,R
71	F,L,I,S	144	K,R,A
72	S,C,G,A,D,K	145	Y,C,H
73	D,E,Q,N	146	H,D

The second structure tested relied on data compiled from three different data sources to address the frequency of any nucleotide being replaced by mutation to the other three. These estimate were derived from different collections of proteins. This structure results in three assessments of nucleotide mutation potential and amino acid possibility assessment. The transition probabilities are listed in Table 3.3.

Table 3.3
DNA Nucleotide Change Frequency

Transition	Dayhoff frequency	Zuckerkandl frequency	Fitch frequency
A=>C	.0244	.0610	.0113
A=>G	.0731	.0360	.0000
A=>T	.0488	.0690	.0602
C=>A	.0122	.0850	.0458
C=>G	.0854	.0980	.0989
C=>T	.2927	.1590	.0960
G=>A	.0610	.0380	.0277
G=>C	.0976	.0920	.0635
G=>T	.0732	.0890	.1995
T=>A	.0366	.0580	.1140
T=>C	.1098	.1210	.1237
T=>G	.0854	.0940	.1694

The third structure conformed to a first order Ising model in which the ordered nucleotide composition of the two nearest neighbors determined what the transition probability at any particular nucleotide site on the genome. Again, amino acid possibility assessment was made before any nucleotide change was allowed to occur. The transition probabilities are listed in Table 3.4.

Table 3.4
DNA Nearest Neighbor Nucleotide Change Frequency

5'=>3'	A=>A	A=>C	A=>G	A=>T	C=>A	C=>C	C=>G	C=>T
A_A	.9946	.00016	.00175	.00349	.00018	.9978	.00180	.00024
A_C	.9901	.00198	.00713	.00079	.00061	.9935	.00427	.00163
A_G	.9957	.00217	.00120	.00193	.00094	.9913	.00126	.00650
A_T	.9872	.00230	.00722	.00328	.00125	.9840	.00847	.00627
C_A	.9948	.00035	.00247	.00247	.00072	.9976	.00168	.00000
C_C	.9901	.00194	.00699	.00097	.00063	.9935	.00440	.00147
C_G	.9947	.00198	.00110	.00221	.00093	.9913	.00124	.00652
C_T	.9874	.00342	.00315	.00603	.00032	.9933	.00260	.00378
G_A	.9946	.00135	.00135	.00270	.00000	.9936	.00260	.00378
G_C	.9900	.00198	.00713	.00079	.00061	.9935	.00427	.00163
G_G	.9947	.00217	.00120	.00193	.00094	.9913	.00126	.00650
G_T	.9872	.00199	.00796	.00284	.00125	.9840	.00847	.00627
T_A	.9947	.00035	.00247	.00247	.00032	.9976	.00208	.00000
T_C	.9901	.00194	.00699	.00097	.00063	.9650	.00440	.00147
T_G	.9947	.00198	.00110	.00221	.00093	.9913	.00124	.00652
T_T	.9872	.00259	.00484	.00536	.00034	.9913	.00394	.00442
5'=>3'	G=>A	G=>C	G=>G	G=>T	T=>A	T=>C	T=>G	T=>T
A_A	.00151	.01389	.9840	.00060	.00311	.00206	.00033	.9945
A_C	.00692	.00053	.9867	.00585	.00101	.00730	.00579	.9859
A_G	.00185	.00238	.9926	.00317	.00152	.00532	.00196	.9912
A_T	.00176	.00821	.9871	.00293	.00137	.01164	.00479	.9822
C_A	.00295	.01263	.9840	.00042	.01333	.00000	.00263	.9840
C_C	.00640	.00049	.9867	.00640	.00053	.00904	.00393	.9865
C_G	.00167	.00215	.9926	.00358	.00157	.00876	.00207	.9876
C_T	.00165	.00660	.9871	.00465	.00072	.00417	.00251	.9926
G_A	.00205	.01231	.9840	.00164	.00467	.00050	.00033	.9945
G_C	.00692	.00053	.9867	.00585	.00101	.00730	.00579	.9859
G_G	.00185	.00228	.9926	.00317	.00152	.00532	.00196	.9912
G_T	.00183	.00879	.9871	.00228	.00123	.01043	.00614	.9822
T_A	.00215	.01354	.9840	.00031	.01333	.00000	.00267	.9840
T_C	.00640	.00049	.9867	.00650	.00101	.00504	.00746	.9865
T_G	.00167	.00215	.9926	.00358	.00231	.00707	.00303	.9876
T_T	.00227	.00765	.9871	.00298	.00072	.00417	.00251	.9926

When the possibility assessment was favorable, the transition is recorded and the new nucleotide will be substituted into the chain. When the possibility assessment did not reveal evidence for the particular amino acid appearing at that position of the hemoglobin chain, the nucleotide will be left without change and the failure to be able to change the nucleotide is recorded.

Many types of information can be recorded from the model. In addition to writting out checks to validate the input data, the model can be used to write out information to trace the point mutations that occurred sequentially from the start of the experiment. The information on transition rates for both amino acids and nucleic acids is output as well as the number of times that possibility assessment did not allow the transition. The number of times that the mutation of an nucleic acid or an amino acid back mutates to an earlier configuration at a location along the chain. Other recorded data includes the simularity of the resulting amino acid sequence with the starting protein chains of human, rabbit, and ancestrial beta hemoglobin. The amino acid and nucleotide sequences entered at each location was also put into data files for storage. This information was stored into intermediate files to be used by the Statistical Package for Social Scientists(SPSS) for data analysis and computations.

Statistical tests were used to evaluate the results of the simulation. Linear regression and analysis of variance were used to help understand the relationships that were revealed during the experiment. Review and categorization of the results was used to examine relationships and to determine the applicability of different techniques and the implications of the results of this simulation.

CHAPTER IV

RESULTS

The simulation model used for this study was implemented and tested on the Cyber computer system used by the School of Engineering at the Air Force Institute of Technology. Model verification was conducted. Data collection consisted of 1275 runs of the model on the IBM 370/155 operated by the Human Engineering Division of the Air Force Aerospace Medical Research Laboratory. 425 runs of the model were made for each of the three initial hemoglobin DNA sequences to be examined. The number of iterations selected were randomly determined out of three groups. A stream of random digits between 0 and 9 were used to establish the number of iterations(probability assessment of a mutation at each position along the entire chain) to be used. The three groups were formed by sequentially multiplying the sum of the chosen random digit and 1 by 1, 10, and 1000. This resulted in a stream of iterations which varied between 1 and 1000. Random number streams were generated within the model for the probabalistic determination of a mutation occuring at any location.

Statistical testing of the random digit stream revealed no trends or bias. Verification included of examining and

comparing the resultant nucleotide transition frequencies with the transition tables for each of the methods used in the model. There was no observable abnormality and the Chi Square test revealed no significant difference at the 0.05 level. The pattern of changes in amino acids produced in the model appeared to be consistent with the pattern of mutations observed by phenotypic studies of abnormal hemoglobin in vivo. The amino acid mutations produced by the model resulted in primary sequences indistinguishible from primary sequences observed in different species.

Table 4.1
Nucleotide Transition Anova

Transition	Effect	Significance Level
A=>C	Interations	<0.001
	Method	<0.001
A=>G	Interations	<0.001
	Method	<0.001
A=>T	Interations	<0.001
	Method	<0.001
C=>A	Interations	<0.001
	Method	<0.001
C=>G	Interations	<0.001
	Method	<0.001
C=>T	Interations	<0.001
	Method	<0.001
G=>A	Interations	<0.001
	Method	<0.001
	Hemoglobin	<0.01
G=>C	Interations	<0.001
	Method	<0.001
G=>T	Interations	<0.001
	Method	<0.001
T=>A	Interations	<0.001
	Method	<0.001
T=>C	Interations	<0.001
	Method	<0.001
T=>G	Interations	<0.001
	Method	<0.001

The results of the anova used to examine the changes in nucleotides observed in the model can be found in table 4.1.

The anova revealed that both the method being used to generate transition probabilities and the number of iterations of the model has a consistently significan effect on the transition of a nucleotide to one of the other three possible nucleotides. Hemoglobin starting chain was only found significant for the transition of guanine to adenine.

The results of the anova conducted to examine the transitions between amino acids can be found in table 4.2.

Table 4.2
Amino Acid Transition Anova

Transition	Effects (Significance Level)		
	Interations	Method	Hemoglobin
G=>A	<0.001	<0.001	
G=>S	<0.001	<0.001	
G=>V	<0.001	<0.001	
G=>E	<0.001	<0.001	<0.001
G=>D	<0.001	<0.001	<0.05
G=>R	<0.001	<0.001	
G=>C	<0.001	<0.001	
G=>W	<0.001		
A=>G	<0.001	<0.001	
A=>S	<0.001	<0.001	
A=>V	<0.001	<0.001	
A=>K	<0.001	<0.001	
A=>T	<0.001	<0.001	
A=>E	<0.001	<0.001	<0.05
A=>P	<0.001	<0.001	<0.001
A=>D	<0.001	<0.001	<0.001
A=>R	<0.001	<0.001	<0.001
A=>M	<0.001	<0.001	<0.001
L=>S	<0.001	<0.001	
L=>V	<0.001	<0.001	
L=>P	<0.001	<0.001	<0.001
L=>I	<0.001	<0.001	
L=>R	<0.001	<0.001	
L=>Q	<0.001	<0.001	
L=>F	<0.001	<0.001	
L=>H	<0.001	<0.001	

Table 4.2 Continued

Transition	Effects (Significance Level)		
	Interations	Method	Hemoglobin
L=>M	<0.001	<0.001	<0.001
L=>W	<0.001	<0.001	
S=>G	<0.001	<0.001	
S=>A	<0.001	<0.001	
S=>L	<0.001	<0.001	
S=>T	<0.001	<0.001	
S=>P	<0.001	<0.01	<0.001
S=>I	<0.001	<0.001	
S=>R	<0.001	<0.001	
S=>N	<0.001	<0.001	<0.001
S=>F	<0.001	<0.001	
S=>Y	<0.001	<0.00.	
S=>C	<0.001	<0.001	
S=>W	<0.001	<0.001	
V=>G	<0.001	<0.001	
V=>A	<0.001	<0.001	
V=>L	<0.001	<0.001	
V=>E	<0.001	<0.001	<0.05
V=>D	<0.001	<0.001	
V=>I	<0.001	<0.001	<0.001
V=>F	<0.001	<0.001	
V=>M	<0.001	<0.01	
K=>A	<0.001	<0.001	
K=>T	<0.001	<0.001	
K=>E	<0.001	<0.001	
K=>I	<0.001	<0.001	<0.05
K=>R	<0.001	<0.001	
K=>N	<0.001	<0.001	
K=>Q	<0.001	<0.001	
K=>M	<0.001	<0.001	
T=>A	<0.001	<0.001	
T=>S	<0.001	<0.001	<0.001
T=>K	<0.001	<0.001	<0.001
T=>P	<0.001	<0.001	<0.05
T=>I	<0.001	<0.001	
T=>R	<0.001	<0.001	
T=>N	<0.001	<0.001	
F=>G	<0.001	<0.001	
F=>A	<0.001	<0.001	
F=>V	<0.001	<0.001	
F=>K	<0.001	<0.001	
F=>D	<0.001	<0.001	<0.001
F=>Q	<0.001	<0.001	
P=>A	<0.001	<0.001	<0.001
P=>L	<0.001	<0.001	
P=>S	<0.001	<0.001	<0.001
P=>T	<0.001	<0.001	
P=>R	<0.001	<0.001	

Table 4.2 Continued

Transition	Effects (Significance Level)		
	Interations	Method	Hemoglobin
P=>Q	<0.001	<0.001	
P=>H	<0.001	<0.001	
D=>G	<0.001	<0.001	
D=>A	<0.001	<0.001	
D=>V	<0.001	<0.001	
D=>E	<0.001	<0.001	
D=>N	<0.001	<0.001	
D=>Y	<0.001	<0.001	
D=>H	<0.001	<0.001	
I=>L	<0.001	<0.001	
I=>S	<0.001	<0.001	<0.05
I=>V	<0.001	<0.001	
I=>K	<0.001	<0.001	<0.001
I=>T	<0.001	<0.001	
I=>N	<0.001	<0.001	
I=>F	<0.001	<0.001	
I=>M	<0.001	<0.01	
R=>G	<0.001	<0.001	<0.05
R=>A	<0.001	<0.001	
R=>L	<0.001	<0.001	
R=>S	<0.001	<0.001	
R=>K	<0.001	<0.001	<0.05
R=>T	<0.001	<0.001	
R=>P	<0.001	<0.001	
R=>I	<0.001	<0.01	
R=>Q	<0.001	<0.001	<0.01
R=>C	<0.001	<0.001	<0.05
R=>H	<0.001	<0.001	
R=>M	<0.001	<0.001	
R=>W	<0.001	<0.001	
N=>S	<0.001	<0.001	
N=>K	<0.001	<0.001	
N=>T	<0.001	<0.001	<0.05
N=>D	<0.001	<0.001	
N=>I	<0.001	<0.001	
N=>Y	<0.001	<0.05	
N=>H	<0.001	<0.001	
Q=>L	<0.001	<0.001	
Q=>K	<0.001	<0.001	
Q=>E	<0.001	<0.001	
Q=>P	<0.001	<0.001	<0.001
Q=>R	<0.001	<0.001	
Q=>H	<0.001	<0.001	
F=>L	<0.001	<0.001	
F=>S	<0.001	<0.001	
F=>V	<0.001	<0.001	
F=>I	<0.001	<0.001	
F=>Y	<0.001	<0.001	

Table 4.2 Continued

Transition	Effects (Significance Level)		
	Interations	Method	Hemoglobin
F=>C	<0.001	<0.001	<0.05
Y=>S	<0.001	<0.001	
Y=>D	<0.001	<0.001	
Y=>N	<0.001	<0.001	
Y=>F	<0.001	<0.05	
Y=>C	<0.001	<0.001	<0.001
Y=>H	<0.001	<0.001	
C=>G	<0.001	<0.001	
C=>S	<0.001	<0.001	<0.001
C=>R	<0.001		
C=>F	<0.001	<0.001	
C=>Y	<0.001	<0.001	
H=>L	<0.001	<0.001	
H=>P	<0.001	<0.001	
H=>D	<0.001	<0.001	
H=>R	<0.001	<0.001	
H=>N	<0.001	<0.001	
H=>Q	<0.001	<0.001	
H=>Y	<0.001	<0.001	
M=>A	<0.001	<0.001	
M=>L	<0.001	<0.001	
M=>V	<0.001	<0.001	
M=>K	<0.001		<0.001
M=>I	<0.001		
M=>R	<0.001	<0.01	<0.05
W=>G		<0.001	
W=>L	<0.001	<0.001	
W=>S	<0.001	<0.001	
W=>R	<0.001	<0.001	

As is seen in examining the results of the nucleotide anova, both the number of iterations of the chain and the method of assessing the transition probabilities resulted in overwhelmingly significant effects. Hemoglobin was found to be a significant effect for several of the amino acid transitions.

Table 4.3 presents information on the frequency of the transitons observed in the position and iteration averaged values of the nucleotide.

Table 4.3
Average Nucleotide Transition Frequency

	Random	Dayhoff	Zuckerkandl	Fitch	Nearest-Neighbor
Allowed Change	49.43	117.90	108.75	111.55	43.94
Repeated Change	6.70	38.45	36.27	38.03	6.34
Rejected Change	211.58	542.46	526.98	530.59	197.91

Table 4.4 contains the results from the regression of the value of the positioned averaged transition of nucleotides.

Table 4.4
Average Nucleotide Transition Regression

Intercept/ Slope	Random	Dayhoff	Zuckerkandl	Fitch	Nearest-Neighbor
Allowed	1.311	3.144	5.296	3.434	2.236
Change	.2254	.5375	.4846	.5064	.1953
Repeated	-1.515	-7.924	-6.721	-6.073	-1.454
Change	.0385	.2172	.2013	.2108	.0365
Rejected	-2.160	0.000	0.396	-2.531	-2.792
Change	1.160	2.944	2.858	2.894	1.089

In these tables, the variable that tracks allowed change is incremented every time that a nucleotide change produces a reasonable amino acid at the particular amino acid position coded for by the nucleotide. Repeated change refers to any nucleotide change for which the nucleotide previously had the same base at some earlier time during the run of the model. Rejected change is incremented whenever the proposed nucleotide transition would result in the coding of an amino acid residue that has not been previously

associated with any of the polymorphs, abnormal hemoglobin variants, or species with sequenced hemoglobin in Atlas of Protein Sequence and Structure at that particular location.

Table 4.5 presents information on the frequency of the transitons observed in the position and iteration averaged values of the amino acid residues.

Table 4.5
Average Amino Acid Transition Frequency

	Random	Dayhoff	Zuckerkandl	Fitch	Nearest-Neighbor
Accepted Change	42.38	105.40	97.97	100.45	41.12
Repeated Amino Acid	49.42	117.87	108.75	111.55	43.94

Table 4.6 contains the results from the regression of the value of the positioned averaged transition of amino acid residues.

Table 4.6
Average Amino Acid Transition Regression

Intercept/ Slope	Random	Dayhoff	Zuckerkandl	Fitch	Nearest-Neighbor
Accepted	1.837	1.972	4.527	2.772	2.065
Change	.2177	.5553	.5017	.5244	.2097
Repeated	1.311	3.144	5.256	3.434	2.236
Amino Acid	.2254	.5375	.4846	.5064	.1953

In the two preceeding tables, accepted changes are the result of nucleotide changes that were compatible with coding for accepted amino acids at the appropriate position. The repeated amino acid line of the tables presents that subset of the accepted amino acid changes that result in an

amino acid that was previously found during a particular simulation run at the same position of the protein chain.

Table 4.7 contains a listing of the regression of transition frequency as a function of interation listed by nucleotide position.

Table 4.7
Nucleotide Transition Regression

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
1	None Seen	No Repeats	None Rejected
2	0.0240	-0.0160	0.0679
	0.0015	0.0004	0.0056
3	-0.0291	-0.0287	0.1318
	0.0016	0.0007	0.0055
4	-0.0094	-0.0033	-0.0235
	0.0001	0.0000	0.0025
5	-0.0410	-0.0259	0.1093
	0.0015	0.0006	0.0058
6	0.0438	-0.0035	-0.2064
	0.0018	0.0002	0.0054
7	None Seen	No Repeats	0.1686
			0.0022
8	-0.0214	-0.0014	0.0231
	0.0008	0.0000	0.0059
9	-0.0260	-0.0125	0.0624
	0.0004	0.0002	0.0060
10	-0.0033	-0.0004	0.0386
	0.0000	0.0000	0.0034
11	0.0463	-0.0016	0.0294
	0.0009	0.0000	0.0081
12	0.0039	0.0016	-0.0365
	0.0002	0.0001	0.0076
13	-0.0000	No Repeats	-0.0456
	0.0000		0.0015
14	0.0608	-0.0176	-0.1250
	0.0011	0.0005	0.0066
15	0.0999	0.0016	-0.0358
	0.0012	0.0001	0.0056
16	0.0885	-0.0000	-0.0540
	0.0008	0.0000	0.0028
17	-0.0087	-0.0074	-0.0406
	0.0004	0.0002	0.0050

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
18	0.0653	0.0018	-0.1654
	0.0005	0.0001	0.0068
19	-0.0018	-0.0100	-0.0092
	0.0010	0.0005	0.0011
20	0.1507	-0.0000	-0.0907
	0.0011	0.0000	0.0068
21	-0.0056	-0.0084	0.1703
	0.0018	0.0010	0.0066
22	-0.1228	-0.0770	0.0410
	0.0030	0.0015	0.0018
23	-0.0120	-0.0818	0.1544
	0.0034	0.0017	0.0076
24	-0.0360	-0.0111	-0.0565
	0.0008	0.0003	0.0098
25	-0.0072	-0.0012	-0.0216
	0.0001	0.0000	0.0008
26	0.0145	-0.0117	-0.0622
	0.0014	0.0006	0.0046
27	-0.0066	-0.0056	0.0551
	0.0009	0.0002	0.0041
28	None Seen	No Repeats	-0.0043
			0.0022
29	0.0470	-0.0080	-0.1331
	0.0010	0.0002	0.0062
30	0.0580	No Repeats	-0.1106
	0.0004		0.0064
31	None Seen	No Repeats	-0.0449
			0.0022
32	0.0382	0.0004	0.0196
	0.0006	0.0000	0.0062
33	-0.0041	-0.0087	-0.0257
	0.0006	0.0003	0.0065
34	None Seen	No Repeats	-0.0902
			0.0021
35	None Seen	No Repeats	0.0538
			0.0056
36	None Seen	No Repeats	-0.1616
			0.0077
37	None Seen	No Repeats	-0.0440
			0.0009
38	0.0010	-0.0006	-0.1044
	0.0001	0.0000	0.0066
39	-0.0454	-0.0504	0.0850
	0.0029	0.0013	0.0045
40	None Seen	No Repeats	-0.0331
			0.0007
41	-0.0200	-0.0086	-0.0003
	0.0007	0.0002	0.0045

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
42	-0.0136	-0.0366	-0.0745
	0.0025	0.0012	0.0054
43	None Seen	No Repeats	-0.0008
			0.0059
44	0.0485	-0.0188	0.1758
	0.0018	0.0007	0.0067
45	-0.0143	-0.0099	0.0086
	0.0009	0.0003	0.0062
46	-0.0230	-0.0179	0.0039
	0.0008	0.0004	0.0013
47	0.0643	-0.0200	0.0545
	0.0021	0.0010	0.0069
48	-0.0003	-0.0084	0.1020
	0.0014	0.0008	0.0052
49	None Seen	No Repeats	-0.0427
			0.0047
50	-0.0459	-0.0284	0.1272
	0.0014	0.0006	0.0062
51	0.0556	No Repeats	-0.1116
	0.0011		0.0058
52	-0.0207	-0.0015	-0.0292
	0.0007	0.0002	0.0006
53	-0.0170	-0.0166	-0.0175
	0.0020	0.0003	0.0059
54	-0.0414	-0.0234	-0.0246
	0.0011	0.0005	0.0080
55	0.0093	- 0.0008	-0.0321
	0.0002	0.0000	0.0026
56	-0.0248	-0.0234	-0.1041
	0.0015	0.0008	0.0060
57	0.0978	-0.0309	-0.0850
	0.0030	0.0009	0.0065
58	0.0073	-0.0000	-0.0464
	0.0001	0.0000	0.0021
59	0.0567	-0.0062	0.0215
	0.0006	0.0001	0.0041
60	-0.0192	-0.0311	0.0449
	0.0018	0.0008	0.0058
61	None Seen	No Repeats	0.0108
			0.0019
62	0.0709	-0.0555	-0.0782
	0.0031	0.0013	0.0054
63	-0.0170	-0.0309	-0.1159
	0.0016	0.0008	0.0073
64	None Seen	No Repeats	-0.0460
			0.0032
65	-0.0080	-0.0037	-0.1562
	0.0002	0.0001	0.0093

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
66	-0.0012	No Repeats	-0.0388
	0.0000		0.0066
67	-0.0048	-0.0020	-0.0175
	0.0009	0.0003	0.0007
68	-0.0118	-0.0123	0.0030
	0.0007	0.0002	0.0034
69	0.0984	-0.1056	-0.0030
	0.0071	0.0043	0.0023
70	-0.0008	0.0036	-0.0262
	0.0004	0.0001	0.0014
71	0.1193	0.0130	0.1506
	0.0019	0.0008	0.0057
72	-0.0215	-0.0206	0.0155
	0.0014	0.0008	0.0071
73	-0.0243	-0.0087	0.0186
	0.0009	0.0002	0.0030
74	0.0513	-0.0567	0.0511
	0.0030	0.0012	0.0055
75	-0.0412	-0.0480	0.0079
	0.0024	0.0009	0.0045
76	-0.0247	-0.0045	0.0776
	0.0015	0.0004	0.0030
77	0.0231	-0.0635	0.0330
	0.0030	0.0015	0.0057
78	-0.0161	-0.0832	-0.1682
	0.0040	0.0022	0.0040
79	-0.0025	-0.0012	0.0136
	0.0000	0.0000	0.0014
80	-0.0425	-0.0814	0.0052
	0.0037	0.0019	0.0043
81	-0.0317	-0.0180	0.0401
	0.0017	0.0007	0.0066
82	-0.0375	-0.0117	-0.0416
	0.0011	0.0002	0.0008
83	0.0044	-0.0135	-0.0184
	0.0015	0.0002	0.0065
84	-0.0378	-0.0258	0.0981
	0.0010	0.0004	0.0071
85	-0.0293	-0.0279	-0.0482
	0.0019	0.0009	0.0023
86	0.1172	-0.0174	-0.1215
	0.0022	0.0010	0.0068
87	-0.0129	-0.0441	-0.0985
	0.0025	0.0011	0.0068
88	None Seen	No Repeats	0.1238
			0.0023
89	0.0008	-0.0185	-0.0172
	0.0020	0.0004	0.0078

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
90	0.0103	-0.0301	0.1865
	0.0022	0.0010	0.0045
91	-0.0019	-0.0006	0.0537
	0.0000	0.0000	0.0011
92	-0.0115	-0.0161	0.0829
	0.0009	0.0004	0.0036
93	-0.0110	-0.0129	0.1076
	0.0002	0.0002	0.0061
94	None Seen	No Repeats	-0.0673
			0.0021
95	-0.0244	-0.0132	0.0683
	0.0017	0.0003	0.0054
96	-0.0507	-0.0299	-0.0461
	0.0011	0.0005	0.0063
97	-0.0031	-0.0012	-0.0704
	0.0001	0.0000	0.0017
98	-0.0032	-0.0161	-0.0433
	0.0013	0.0005	0.0045
99	-0.0260	-0.0134	-0.0892
	0.0010	0.0005	0.0061
100	None Seen	No Repeats	-0.0051
			0.0002
101	0.0060	-0.0186	-0.1118
	0.0020	0.0006	0.0046
102	0.0193	-0.0160	0.0385
	0.0014	0.0004	0.0078
103	None Seen	No Repeats	0.0145
			0.0048
104	0.0115	0.0066	-0.0791
	0.0002	0.0001	0.0069
105	0.0018	-0.0000	0.0456
	0.0001	0.0000	0.0050
106	-0.0428	-0.0257	-0.0138
	0.0015	0.0006	0.0004
107	0.0480	-0.0164	0.0581
	0.0020	0.0008	0.0041
108	0.1660	-0.0615	0.0822
	0.0043	0.0018	0.0056
109	None Seen	No Repeats	-0.0484
			0.0039
110	-0.0518	-0.0382	0.0015
	0.0015	0.0008	0.0061
111	0.0393	-0.0025	-0.0255
	0.0013	0.0000	0.0046
112	0.0048	No Repeats	-0.0139
	0.0001		0.0015
113	0.0685	0.0114	0.0073
	0.0017	0.0003	0.0044

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
114	0.0153	-0.00562	0.0671
	0.0004	0.0003	0.0104
115	None Seen	No Repeats	0.1773
			0.0018
116	0.1958	0.0077	0.0145
	0.0033	0.0015	0.0044
117	-0.0411	-0.0272	0.0012
	0.0012	0.0007	0.0077
118	0.0024	No Repeats	-0.0328
	0.0000		0.0027
119	0.0034	-0.0031	0.0030
	0.0006	0.0001	0.0095
120	0.0483	-0.0113	0.0680
	0.0013	0.0007	0.0052
121	-0.0025	-0.0012	-0.0068
	0.0000	0.0000	0.0031
122	-0.0298	-0.0171	-0.0125
	0.0008	0.0004	0.0036
123	0.0313	-0.0221	-0.0510
	0.0019	0.0009	0.0057
124	None Seen	No Repeats	0.0522
			0.0025
125	None Seen	No Repeats	0.0283
			0.0037
126	0.0588	-0.0720	0.1128
	0.0041	0.0020	0.0038
127	0.0136	-0.0017	0.0274
	0.0003	0.0000	0.0023
128	0.0323	-0.0015	-0.0116
	0.0016	0.0002	0.0063
129	-0.0127	-0.0066	-0.0463
	0.0006	0.0002	0.0062
130	None Seen	No Repeats	-0.0294
			0.0043
131	-0.0121	No Repeats	0.0221
	0.0012		0.0058
132	-0.0031	No Repeats	-0.0117
	0.0001		0.0039
133	None Seen	No Repeats	0.0003
			0.0040
134	None Seen	No Repeats	0.0621
			0.0065
135	None Seen	No Repeats	0.0969
			0.0058
136	-0.0979	-0.0439	0.0279
	0.0030	0.0012	0.0010
137	0.0893	0.0101	-0.1334
	0.0015	0.0005	0.0069

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
138	-0.0012	No Repeats	-0.0873
	0.0000		0.0092
139	None Seen	No Repeats	-0.0189
			0.0033
140	-0.0158	-0.0131	-0.1156
	0.0009	0.0005	0.0086
141	0.0316	-0.0031	-0.0570
	0.0007	0.0001	0.0069
142	-0.0161	No Repeats	0.0626
	0.0004		0.0027
143	-0.0155	-0.0006	0.1275
	0.0004	0.0000	0.0058
144	-0.0050	No Repeats	0.0674
	0.0003		0.0064
145	None Seen	No Repeats	-0.0049
			0.0001
146	0.0024	-0.0000	-0.1568
	0.0000	0.0000	0.0083
147	0.0146	-0.0000	-0.0180
	0.0001	0.0000	0.0069
148	None Seen	No Repeats	0.0566
			0.0015
149	0.0000	No Repeats	-0.1345
	0.0000		0.0084
150	None Seen	No Repeats	-0.1076
			0.0064
151	None Seen	No Repeats	-0.0176
			0.0010
152	0.0123	-0.0008	0.0670
	0.0003	0.0001	0.0051
153	0.0403	-0.0188	0.0262
	0.0013	0.0003	0.0058
154	-0.1360	-0.1065	0.0043
	0.0042	0.0020	0.0010
155	0.0227	-0.0039	-0.0897
	0.0004	0.0001	0.0080
156	0.0131	-0.0023	-0.0663
	0.0003	0.0001	0.0067
157	-0.0483	-0.0279	0.1042
	0.0018	0.0008	0.0005
158	-0.0027	-0.0017	-0.0748
	0.0001	0.0000	0.0079
159	0.0774	-0.0260	0.1247
	0.0025	0.0016	0.0049
160	0.0030	-0.0000	0.0218
	0.0001	0.0000	0.0014
161	0.0267	No Repeats	0.0038
	0.0001		0.0064

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
162	None Seen	No Repeats	-0.1115
			0.0080
163	None Seen	No Repeats	0.1657
			0.0081
164	None Seen	No Repeats	0.0346
			0.0050
165	None Seen	No Repeats	0.0589
			0.0082
166	-0.0004	No Repeats	-0.0295
	0.0000		0.0023
167	0.0034	-0.0623	0.0002
	0.0029	0.0017	0.0042
168	0.0102	-0.0217	-0.0905
	0.0009	0.0003	0.0072
169	None Seen	No Repeats	-0.0571
			0.0047
170	None Seen	No Repeats	0.0160
			0.0080
171	None Seen	No Repeats	-0.0512
			0.0091
172	None Seen	No Repeats	-0.0643
			0.0020
173	-0.0638	-0.0636	-0.0292
	0.0022	0.0016	0.0075
174	0.0895	No Repeats	-0.0263
	0.0010		0.0072
175	0.1249	No Repeats	-0.1250
	0.0008		0.0042
176	0.0502	-0.0190	-0.1460
	0.0009	0.0003	0.0076
177	None Seen	No Repeats	-0.0490
			0.0078
178	-0.0098	-0.0061	0.0098
	0.0001	0.0001	0.0025
179	-0.0241	-0.0037	-0.0352
	0.0006	0.0001	0.0061
180	0.0324	No Repeats	0.0907
	0.0007		0.0078
181	None Seen	No Repeats	-0.0440
			0.0028
182	0.0275	-0.0019	0.0128
	0.0010	0.0000	0.0071
183	-0.0119	-0.0050	0.0982
	0.0014	0.0005	0.0061
184	-0.0883	-0.0407	0.0233
	0.0027	0.0009	0.0014
185	0.0773	-0.0019	-0.1211
	0.0012	0.0000	0.0069

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
186	-0.0589	-0.0611	-0.0389
	0.0023	0.0015	0.0051
187	None Seen	No Repeats	0.0635
			0.0027
188	-0.0569	-0.0272	0.1970
	0.0015	0.0007	0.0068
189	0.0085	-0.0000	-0.1098
	0.0012	0.0000	0.0086
190	None Seen	No Repeats	-0.0767
			0.0017
191	0.0103	-0.0487	0.0366
	0.0021	0.0010	0.0079
192	0.1047	-0.0025	-0.0567
	0.0010	0.0001	0.0076
193	None Seen	No Repeats	-0.0023
			0.0042
194	0.0596	0.0001	-0.0832
	0.0020	0.0010	0.0064
195	0.1308	0.0005	0.0830
	0.0028	0.0015	0.0043
196	None Seen	No Repeats	-0.0677
			0.0031
197	0.0279	No Repeats	-0.0426
	0.0007		0.0062
198	0.0033	No Repeats	0.0568
	0.0000		0.0073
199	None Seen	No Repeats	0.0939
			0.0016
200	0.0695	-0.0160	0.1742
	0.0010	0.0003	0.0051
201	-0.0487	-0.0597	-0.0813
	0.0027	0.0012	0.0065
202	None Seen	No Repeats	0.0721
			0.0021
203	None Seen	No Repeats	0.1042
			0.0060
204	None Seen	No Repeats	0.0227
			0.0063
205	None Seen	No Repeats	-0.0614
			0.0012
206	-0.0604	-0.0418	-0.1538
	0.0012	0.0007	0.0056
207	0.0591	0.0038	-0.0358
	0.0010	0.0001	0.0057
208	-0.0050	-0.0000	0.1785
	0.0001	0.0000	0.0016
209	-0.0353	-0.0025	-0.1131
	0.0013	0.0000	0.0065

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
210	-0.0037	-0.0000	0.1737
	0.0001	0.0000	0.0105
211	0.0587	No Repeats	-0.0441
	0.0008		0.0026
212	0.0036	-0.0033	0.1166
	0.0020	0.0005	0.0039
213	0.0227	-0.0055	0.0342
	0.0005	0.0001	0.0054
214	None Seen	No Repeats	-0.0617
			0.0029
215	-0.0044	-0.0041	-0.0722
	0.0003	0.0001	0.0079
216	0.0032	0.0006	-0.0016
	0.0001	0.0000	0.0092
217	0.0673	No Repeats	-0.0636
	0.0004		0.0024
218	0.0352	-0.0260	0.0754
	0.0023	0.0011	0.0050
219	None Seen	No Repeats	-0.0539
			0.0075
220	-0.0006	No Repeats	0.0300
	0.0000		0.0010
221	0.0853	-0.0021	-0.0740
	0.0013	0.0001	0.0064
222	None Seen	No Repeats	0.0138
			0.0089
223	-0.0218	-0.0043	0.0336
	0.0004	0.0001	0.0005
224	-0.0173	-0.0012	0.0278
	0.0010	0.0000	0.0052
225	-0.0203	-0.0043	0.1336
	0.0004	0.0001	0.0061
226	-0.0385	-0.0183	-0.0539
	0.0014	0.0004	0.0019
227	0.0575	-0.0188	-0.0251
	0.0020	0.0007	0.0051
228	0.0086	-0.0319	0.0011
	0.0017	0.0009	0.0053
229	0.1118	No Repeats	-0.0748
	0.0008		0.0024
230	-0.0426	No Repeats	-0.0756
	0.0021		0.0058
231	-0.0610	-0.0240	0.0754
	0.0010	0.0004	0.0053
232	None Seen	No Repeats	-0.0244
			0.0005
233	-0.0052	-0.0272	0.0196
	0.0012	0.0007	0.0054

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
234	0.0018	-0.0000	0.1055
	0.0001	0.0000	0.0074
235	0.1115	No Repeats	-0.0544
	0.0008		0.0020
236	0.0212	-0.0388	-0.0008
	0.0021	0.0008	0.0057
237	-0.0128	-0.0138	-0.0029
	0.0015	0.0006	0.0068
238	None Seen	No Repeats	-0.0862
			0.0036
239	0.0503	No Repeats	0.0482
	0.0003		0.0059
240	0.0567	No Repeats	-0.0165
	0.0009		0.0089
241	None Seen	No Repeats	0.0661
			0.0012
242	-0.0192	-0.0092	-0.0165
	0.0005	0.0002	0.0063
243	-0.0069	-0.0366	0.0291
	0.0028	0.0015	0.0060
244	0.1090	-0.0106	-0.0427
	0.0012	0.0002	0.0043
245	-0.0006	-0.0031	0.0361
	0.0001	0.0001	0.0077
246	0.0151	-0.0364	0.0180
	0.0021	0.0011	0.0070
247	None Seen	No Repeats	-0.0540
			0.0024
248	0.0278	-0.0532	-0.0539
	0.0023	0.0014	0.0061
249	0.1042	-0.0125	0.0667
	0.0016	0.0009	0.0068
250	0.0433	-0.0056	0.0712
	0.0009	0.0002	0.0017
251	-0.0128	-0.0062	0.0619
	0.0007	0.0003	0.0085
252	0.0044	-0.1361	0.1065
	0.0066	0.0043	0.0047
253	None Seen	No Repeats	-0.0007
			0.0021
254	0.0263	No Repeats	0.0280
	0.0008		0.0064
255	-0.0025	No Repeats	0.0929
	0.0000		0.0055
256	-0.0590	-0.0272	0.0659
	0.0024	0.0007	0.0014
257	0.0016	-0.0710	-0.0398
	0.0033	0.0021	0.0078

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
258	0.0244	-0.0030	0.1344
	0.0003	0.0002	0.0077
259	0.0031	-0.0028	-0.0296
	0.0012	0.0004	0.0011
260	0.0635	-0.0269	-0.0279
	0.0020	0.0007	0.0050
261	0.0181	-0.0016	0.0407
	0.0014	0.0008	0.0055
262	0.0100	No Repeats	0.0595
	0.0002		0.0014
263	-0.0146	-0.0044	0.0470
	0.0007	0.0002	0.0049
264	-0.0138	-0.0037	0.1057
	0.0006	0.0001	0.0053
265	None Seen	No Repeats	-0.0393
			0.0018
266	-0.0394	-0.0296	0.0148
	0.0016	0.0007	0.0074
267	0.0940	No Repeats	-0.0816
	0.0011		0.0060
268	-0.0196	-0.0075	0.0810
	0.0008	0.0003	0.0023
269	0.0746	-0.0157	0.0216
	0.0019	0.0006	0.0083
270	-0.0587	-0.0326	0.0085
	0.0024	0.0009	0.0037
271	0.0018	-0.0000	0.0003
	0.0001	0.0000	0.0016
272	-0.0365	-0.0173	-0.0072
	0.0010	0.0004	0.0061
273	-0.0032	0.0018	0.1048
	0.0002	0.0000	0.0067
274	-0.0055	-0.0025	0.1639
	0.0001	0.0000	0.0062
275	-0.0684	-0.0382	-0.0214
	0.0016	0.0008	0.0067
276	0.0464	-0.0467	-0.1743
	0.0028	0.0009	0.0064
277	-0.0031	No Repeats	0.0102
	0.0001		0.0015
278	0.0307	-0.0049	-0.1415
	0.0009	0.0001	0.0075
279	0.0174	-0.0031	0.0851
	0.0007	0.0001	0.0064
280	0.0052	-0.0032	-0.0254
	0.0004	0.0003	0.0043
281	0.0054	-0.0013	-0.0052
	0.0002	0.0001	0.0073

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
282	0.0263	-0.0001	0.0268
	0.0003	0.0001	0.0086
283	-0.0917	-0.0519	-0.0296
	0.0027	0.0013	0.0026
284	-0.0096	-0.0111	-0.0727
	0.0004	0.0002	0.0078
285	0.0521	-0.0019	0.0460
	0.0011	0.0000	0.0062
286	-0.0333	-0.0142	-0.0176
	0.0006	0.0003	0.0008
287	0.0239	No Repeats	0.0028
	0.0006		0.0050
288	0.0012	-0.0002	0.0568
	0.0006	0.0003	0.0068
289	0.0029		0.0349
	0.0002		0.0015
290	0.0871	-0.0063	-0.0435
	0.0012	0.0006	0.0072
291	0.0277	-0.0204	-0.1257
	0.0021	0.0005	0.0064
292	None Seen	No Repeats	None Rejected
293	-0.0031	o Repeats	-0.0365
	0.0001		0.0062
294	None Seen	No Repeats	-0.0480
			0.0077
295	-0.0694	-0.0306	-0.0664
	0.0017	0.0006	0.0025
296	0.0285	-0.0032	0.0524
	0.0009	0.0003	0.0059
297	0.0152	-0.0111	-0.0036
	0.0018	0.0003	0.0051
298	-0.0752	-0.0253	0.0278
	0.0018	0.0005	0.0014
299	0.0287	-0.0833	0.0422
	0.0038	0.0028	0.0071
300	-0.0024	No Repeats	-0.0675
	0.0000		0.0097
301	0.0152	0.0073	-0.0368
	0.0001	0.0000	0.0036
302	-0.0028	-0.0418	-0.0783
	0.0026	0.0008	0.0047
303	0.0338	No Repeats	0.1787
	0.0002		0.0068
304	None Seen	No Repeats	0.1483
			0.0037
305	-0.0605	-0.0408	0.2168
	0.0028	0.0012	0.0051

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
306	0.0735	-0.0012	-0.0665
	0.0011	0.0000	0.0072
307	None Seen	No Repeats	-0.0701
			0.0033
308	None Seen	No Repeats	0.0412
			0.0045
309	None Seen	No Repeats	-0.0844
			0.0050
310	None Seen	No Repeats	-0.0115
			0.0034
311	0.0236	-0.0007	0.1183
	0.0005	0.0001	0.0076
312	0.0518	-0.0058	0.0973
	0.0009	0.0001	0.0059
313	None Seen	No Repeats	-0.0492
			0.0021
314	-0.0051	No Repeats	-0.1122
	0.0006		0.0056
315	-0.0265	-0.0129	-0.0200
	0.0005	0.0002	0.0049
316	-0.0051	No Repeats	-0.0074
	0.0002		0.0017
317	-0.0140	-0.0049	0.0091
	0.0009	0.0001	0.0044
318	-0.0087	-0.0019	-0.0980
	0.0003	0.0000	0.0046
319	None Seen	No Repeats	-0.0302
			0.0014
320	-0.0631	-0.0482	0.1247
	0.0020	0.0012	0.0090
321	0.0503	No Repeats	0.0285
	0.0016		0.0060
322	-0.0061	-0.0025	0.0015
	0.0001	0.0000	0.0053
323	-0.0392	-0.0222	0.0051
	0.0012	0.0004	0.0093
324	0.0892	-0.0199	-0.0600
	0.0027	0.0006	0.0071
325	None Seen	No Repeats	-0.0241
			0.0013
326	0.0308	0.0024	0.0139
	0.0000	-0.0000	0.0061
327	0.0440	0.0018	-0.0036
	0.0013	0.0001	0.0048
328	0.0158	0.0037	0.1169
	0.0001	0.0000	0.0035
329	0.0060	-0.0006	0.0770
	0.0008	0.0000	0.0058

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
330	-0.0332	-0.0190	-0.0158
	0.0006	0.0003	0.0044
331	-0.0004	No Repeats	-0.0160
	0.0000		0.0002
332	-0.0047	-0.0008	0.0086
	0.0001	0.0000	0.0051
333	-0.0039	-0.0010	-0.1022
	0.0001	0.0000	0.0088
334	None Seen	No Repeats	0.0168
			0.0026
335	-0.0013	-0.0025	-0.0469
	0.0001	0.0001	0.0054
336	0.0610	0.0024	-0.0624
	0.0008	0.0000	0.0070
337	None Seen	No Repeats	-0.0726
			0.0015
338	0.0040	No Repeats	-0.1484
	0.0000		0.0048
339	0.0285	No Repeats	-0.0120
	0.0012		0.0065
340	-0.0062	-0.0025	0.0007
	0.0001	0.0001	0.0007
341	-0.0320	-0.0135	0.0629
	0.0007	0.0002	0.0043
342	0.1032	No Repeats	-0.0902
	0.0011		0.0069
343	None Seen	No Repeats	-0.0382
			0.0012
344	0.0295	0.0073	0.0270
	0.0004	0.0000	0.0058
345	0.0053	0.0012	-0.0122
	0.0000	0.0000	0.0065
346	None Seen	No Repeats	-0.0716
			0.0022
347	None Seen	No Repeats	-0.1222
			0.0070
348	0.0070	No Repeats	-0.0690
	0.0000		0.0075
349	-0.0102	-0.0023	0.1705
	0.0001	0.0000	0.0035
350	0.0407	No Repeats	0.0660
	0.0011		0.0050
351	-0.0078	-0.0025	0.0692
	0.0001	0.0000	0.0076
352	None Seen	No Repeats	-0.0065
			0.0015
353	0.0207	-0.0037	-0.0244
	0.0005	0.0000	0.0062

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
354	0.0140	-0.0074	-0.0329
	0.0010	0.0001	0.0078
355	None Seen	No Repeats	-0.0504
			0.0018
356	-0.0327	-0.0210	-0.0633
	0.0008	0.0004	0.0077
357	0.0201	No Repeats	-0.0385
	0.0005		0.0065
358	None Seen	No Repeats	-0.0317
			0.0041
359	0.0027	-0.0012	0.0626
	0.0005	0.0000	0.0063
360	None Seen	No Repeats	-0.0661
			0.0067
361	None Seen	No Repeats	0.0702
			0.0017
362	0.0669	-0.0049	0.0364
	0.0014	0.0001	0.0080
363	-0.0593	-0.0334	-0.0735
	0.0015	0.0009	0.0061
364	-0.0393	-0.0141	0.0122
	0.0006	0.0002	0.0022
365	-0.0681	-0.0412	0.1755
	0.0014	0.0007	0.0047
366	0.0102	No Repeats	-0.0432
	0.0006		0.0081
367	-0.0572	-0.0222	0.0192
	0.0020	0.0006	0.0018
368	0.0600	-0.0098	-0.0194
	0.0024	0.0005	0.0040
369	0.0006	No Repeats	-0.0320
	0.0000		0.0082
370	None Seen	No Repeats	-0.0357
			0.0012
371	0.0256	-0.0317	0.0276
	0.0017	0.0008	0.0059
372	0.1330	-0.0068	-0.0480
	0.0020	0.0004	0.0068
373	-0.0046	-0.0045	0.0115
	0.0001	0.0001	0.0016
374	0.0559	-0.0218	-0.1633
	0.0019	0.0007	0.0047
375	0.0299	-0.0010	0.0766
	0.0004	0.0000	0.0065
376	0.0000	No Repeats	-0.0319
	0.0000		0.0019
377	-0.0047	0.0012	-0.0238
	0.0008	0.0001	0.0046

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
378	0.0054	0.0048	0.0630
	0.0002	0.0001	0.0074
379	0.0446	No Repeats	-0.0548
	0.0008		0.0020
380	0.0073	-0.0426	-0.0435
	0.0019	0.0010	0.0066
381	-0.0236	-0.0265	0.0968
	0.0012	0.0006	0.0063
382	-0.0037	No Repeats	-0.0182
	0.0001		0.0030
383	0.0069	-0.0012	0.0723
	0.0001	0.0000	0.0079
384	0.0839	-0.0783	0.0225
	0.0034	0.0017	0.0053
385	-0.0066	-0.0012	-0.0946
	0.0001	0.0000	0.0019
386	0.0582	-0.0149	-0.0679
	0.0024	0.0004	0.0045
387	-0.0417	-0.0348	0.0773
	0.0014	0.0008	0.0077
388	None Seen	No Repeats	0.0324
			0.0050
389	-0.0061	No Repeats	-0.1540
	0.0001		0.0078
390	None Seen	No Repeats	0.0833
			0.0075
391	None Seen	No Repeats	-0.1154
			0.0041
392	-0.0245	-0.0246	0.1098
	0.0016	0.0008	0.0077
393	0.0738	-0.0006	0.1109
	0.0013	0.0000	0.0068
394	-0.0166	-0.0151	0.0813
	0.0004	0.0002	0.0068
395	-0.0133	-0.0078	-0.1425
	0.0010	0.0001	0.0086
396	-0.0448	-0.0279	-0.0011
	0.0011	0.0005	0.0061
397	None Seen	No Repeats	-0.0155
			0.0018
398	0.0556	-0.0006	-0.0729
	0.0009	0.0001	0.0058
399	0.0006	-0.0000	-0.1685
	0.0001	0.0000	0.0069
400	None Seen	No Repeats	-0.0020
			0.0003
401	None Seen	No Repeats	-0.0000
			0.0056

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
402	None Seen	No Repeats	-0.2218
			0.0102
403	-0.0093	-0.0043	-0.0291
	0.0002	0.0001	0.0007
404	-0.0219	-0.0068	0.0720
	0.0007	0.0001	0.0065
405	0.0561	-0.0012	0.0662
	0.0011	0.0000	0.0044
406	None Seen	No Repeats	-0.0081
			0.0005
407	0.0619	0.0036	-0.1284
	0.0007	0.0000	0.0058
408	-0.0309	-0.0124	0.0727
	0.0010	0.0004	0.0071
409	-0.0500	-0.0117	-0.0215
	0.0011	0.0002	0.0006
410	-0.0215	-0.0735	-0.0077
	0.0011	0.0002	0.0006
411	-0.0946	-0.0704	-0.1072
	0.0030	0.0017	0.0052
412	-0.0364	-0.0148	0.0179
	0.0008	0.0004	0.0088
413	-0.0569	-0.0250	-0.0182
	0.0021	0.0008	0.0006
414	0.0473	-0.0557	-0.0364
	0.0033	0.0017	0.0077
415	-0.0221	-0.0135	-0.0686
	0.0003	0.0002	0.0034
416	0.0290	0.0024	-0.0758
	0.0000	0.0000	0.0073
417	0.0952	-0.0000	0.0352
	0.0013	0.0001	0.0058
418	-0.0184	-0.0074	-0.0277
	0.0003	0.0001	0.0022
419	0.0102	-0.0222	-0.0072
	0.0018	0.0005	0.0059
420	-0.0181	-0.0307	-0.1104
	0.0015	0.0005	0.0078
421	None Seen	No Repeats	-0.0450
			0.0029
422	0.0582	-0.0037	0.0813
	0.0007	0.0001	0.0069
423	0.0048	No Repeats	0.0086
	0.0001		0.0087
424	None Seen	No Repeats	-0.0207
			0.0010
425	-0.0118	-0.0089	-0.0347
	0.0004	0.0002	0.0076

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
426	None Seen	No Repeats	-0.0663
			0.0067
427	0.0180	No Repeats	-0.1183
	0.0001		0.0039
428	-0.0213	-0.0123	0.0793
	0.0003	0.0002	0.0072
429	0.0042	No Repeats	-0.0209
	0.0001		0.0055
430	None Seen	No Repeats	-0.0503
			0.0034
431	-0.0312	-0.0472	0.0322
	0.0024	0.0012	0.0056
432	0.1037	No Repeats	0.1043
	0.0006		0.0073
433	None Seen	No Repeats	0.0396
			0.0040
434	0.0256	-0.0154	-0.0015
	0.0014	0.0003	0.0063
435	0.0067	-0.0166	-0.0364
	0.0013	0.0002	0.0044
436	None Seen	No Repeats	0.0054
			0.0027
437	-0.0265	-0.0315	-0.1455
	0.0017	0.0007	0.0071
438	-0.0147	-0.0098	0.0123
	0.0002	0.0001	0.0081

Table 4.8 contains the regression analysis by position for the transition of amino acid residues as a function of iteration.

Table 4.8
Amino Acid Transition Regression

Intercept/ Slope	Accepted			Reverse
Amino Acid	Ancestral Change	Human Change	Rabbit Change	Change
1	0.0425	0.0425	0.0425	-0.0051
	0.0009	0.0009	0.0009	0.0031
2	0.0526	0.0526	0.0526	-0.0066
	0.0012	0.0012	0.0012	0.0034
3	0.6671	0.3180	0.6671	-0.0474
	0.0003	0.0004	0.0003	0.0012

Table 4.8 Continued

Intercept/ Slope Amino Acid	Ancestral Change	Accepted Human Change	Rabbit Change	Reverse Change
4	0.3793	0.3793	0.6724	0.0470
	0.0008	0.0008	0.0000	0.0012
5	0.7315	0.7919	0.7503	0.1607
	0.0005	0.0004	0.0004	0.0023
6	0.1434	0.1434	0.1434	0.1450
	0.0012	0.0012	0.0012	0.0017
7	0.1525	0.1525	0.1525	0.1433
	0.0010	0.0010	0.0010	0.0039
8	0.0870	0.0870	0.0870	-0.1708
	0.0012	0.0012	0.0012	0.0072
9	0.6741	0.3623	0.3623	0.0008
	0.0002	0.0001	0.0001	0.0024
10	0.1155	0.1155	0.1155	0.1051
	0.0011	0.0011	0.0011	0.0014
11	0.6670	0.3694	0.3694	0.0341
	0.0001	0.0005	0.0005	0.0013
12	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
13	0.6688	0.3580	0.3580	-0.0440
	0.0004	0.0002	0.0002	0.0029
14	0.0356	0.0356	0.0356	-0.0335
	0.0005	0.0005	0.0005	0.0032
15	0.0635	0.0635	0.0635	0.0342
	0.0008	0.0008	0.0008	0.0027
16	0.0888	0.0888	0.0888	0.0411
	0.0008	0.0008	0.0008	0.0043
17	0.0556	0.0556	0.0556	0.0097
	0.0011	0.0011	0.0011	0.0026
18	0.0170	0.0170	0.0170	-0.0791
	0.0012	0.0012	0.0012	0.1038
19	0.1349	0.1349	0.1349	0.0823
	0.0013	0.0013	0.0013	0.0047
20	0.0805	0.0805	0.0805	0.0447
	0.0010	0.0010	0.0010	0.0025
21	0.4308	0.7365	0.4308	0.0539
	0.0008	0.0004	0.0008	0.0046
22	-0.0031	-0.0031	-0.0031	-0.0093
	0.0001	0.0001	0.0001	0.0002
23	0.1762	0.1762	0.1762	0.0818
	0.0010	0.0010	0.0010	0.0086
24	0.1565	0.1565	0.1565	0.0969
	0.0007	0.0007	0.0007	0.0037
25	0.1565	0.1565	0.1565	-0.0142
	0.0012	0.0012	0.0012	0.0062
26	0.1970	0.1970	0.1970	-0.0177
	0.0010	0.0010	0.0010	0.0085

Table 4.8 Continued

Intercept/ Slope Amino Acid	Ancestral Change	Accepted Human Change	Rabbit Change	Reverse Change
27	0.0762	0.0762	0.0762	-0.0766
	0.0011	0.0011	0.0011	0.0054
28	0.0491	0.0491	0.0491	-0.0709
	0.0009	0.0009	0.0009	0.0036
29	0.1765	0.1765	0.1765	0.0750
	0.0011	0.0011	0.0011	0.0066
30	0.7279	0.3740	0.3740	0.01110
	0.0004	0.0008	0.0008	0.0042
31	0.0170	0.0170	0.0170	-0.0243
	0.0003	0.0003	0.0003	0.0013
32	0.0190	0.0190	0.0190	-0.0752
	0.0007	0.0007	0.0007	0.0027
33	0.0170	0.0170	0.0170	-0.0323
	0.0004	0.0004	0.0004	0.0023
34	0.0884	0.0884	0.0884	0.0253
	0.0014	0.0014	0.0014	0.0034
35	0.0020	0.0020	0.0020	0.0133
	0.0001	0.0001	0.0001	0.0003
36	0.2160	0.2160	0.2160	0.1712
	0.0012	0.0012	0.0012	0.0078
37	0.0442	0.0442	0.0442	-0.0125
	0.0012	0.0012	0.0012	0.0028
38	0.0719	0.0719	0.0719	0.0886
	0.0010	0.0010	0.0010	0.0021
39	0.1794	0.1794	0.1794	0.1547
	0.0008	0.0008	0.0008	0.0044
40	0.0766	0.0766	0.0766	0.0541
	0.0008	0.0008	0.0008	0.0021
41	0.0504	0.0504	0.0504	-0.0010
	0.0007	0.0007	0.0007	0.0028
42	0.1457	0.1457	0.1457	0.0588
	0.0011	0.0011	0.0011	0.0041
43	0.6605	9.6146	9.6146	0.0331
	0.0004	0.0007	0.0007	0.0025
44	-0.0121	-0.0121	-0.0121	-0.0152
	0.0012	0.0012	0.0012	0.0013
45	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
46	0.0714	0.0714	0.0714	-0.0097
	0.0009	0.0009	0.0009	0.0045
47	0.0372	0.0372	0.0372	0.0159
	0.0006	0.0006	0.0006	0.0016
48	-0.0121	-0.0121	-0.0121	-0.0366
	0.0012	0.0012	0.0012	0.0011
49	0.0146	0.0146	0.0146	0.0170
	0.0000	0.0000	0.0000	0.0001

Table 4.8 Continued

Intercept/ Slope Amino Acid	Accepted Ancestral Change	Accepted Human Change	Accepted Rabbit Change	Reverse Change
50	0.3333	0.6667	0.3333	0.0000
	0.0000	0.0000	0.0000	0.0000
51	0.3753	0.7054	0.3753	0.0525
	0.0002	0.0003	0.0002	0.0016
52	0.3634	0.3634	0.7116	-0.1003
	0.0002	0.0002	0.0004	0.0048
53	0.0806	0.0806	0.0806	0.0264
	0.0004	0.0004	0.0004	0.0044
54	0.0267	0.0267	0.0267	0.0297
	0.0001	0.0001	0.0001	0.0002
55	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
56	0.4010	0.4010	0.6562	0.0132
	0.0007	0.0007	0.0001	0.0038
57	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
58	0.0937	0.0937	0.0937	0.0257
	0.0010	0.0010	0.0010	0.0033
59	0.2034	0.2034	0.2034	0.1751
	0.0012	0.0012	0.0012	0.0017
60	0.0282	0.0282	0.0282	-0.0015
	0.0008	0.0008	0.0008	0.0015
61	0.0275	0.0275	0.0275	0.0156
	0.0009	0.0009	0.0009	0.0024
62	0.0823	0.0823	0.0823	0.0700
	0.0011	0.0011	0.0011	0.0062
63	0.0085	0.0085	0.0085	-0.0484
	0.0012	0.0012	0.0012	0.0027
64	0.1735	0.1735	0.1735	0.1149
	0.0012	0.0012	0.0012	0.0031
65	0.1442	0.1442	0.1442	0.1903
	0.0008	0.0008	0.0008	0.0048
66	0.0299	0.0299	0.0299	0.0312
	0.0006	0.0006	0.0006	0.0007
67	0.1097	0.1097	0.1097	0.0208
	0.0012	0.0012	0.0012	0.0036
68	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
69	0.3827	0.3827	0.6649	-0.0013
	0.0008	0.0008	0.0001	0.0022
70	-0.0290	-0.0290	-0.0290	-0.0440
	0.0012	0.0012	0.0012	0.0016
71	0.1141	0.1141	0.1141	0.0850
	0.0013	0.0013	0.0013	0.0033
72	0.6660	0.3345	0.3345	-0.0012
	0.0002	0.0001	0.0001	0.0004

Table 4.8 Continued

Intercept/ Slope Amino Acid	Ancestral Change	Accepted Human Change	Rabbit Change	Reverse Change
73	0.4418	0.4418	0.6212	0.1025
	0.0008	0.0008	0.0001	0.0027
74	0.0860	0.0860	0.0860	0.0847
	0.0012	0.0012	0.0012	0.0013
75	-0.0112	-0.0112	-0.0112	-0.0594
	0.0010	0.0010	0.0010	0.0019
76	0.7060	0.7009	0.7093	0.0275
	0.0040	0.0001	0.0004	0.0051
77	0.1225	0.1225	0.1225	0.0383
	0.0013	0.0013	0.0013	0.0039
78	0.0343	0.0343	0.0343	-0.0034
	0.0004	0.0004	0.0004	0.0015
79	0.1927	0.1927	0.1927	0.1199
	0.0012	0.0012	0.0012	0.0044
80	0.1069	0.1069	0.1069	0.1069
	0.0012	0.0012	0.0012	0.0012
81	0.0460	0.0460	0.0460	-0.0261
	0.0006	0.0006	0.0006	0.0033
82	0.1869	0.1869	0.1869	0.1234
	0.0012	0.0012	0.0012	0.0035
83	0.1624	0.1624	0.1624	0.1321
	0.0008	0.0008	0.0008	0.0039
84	0.1999	0.1999	0.1999	0.0035
	0.0009	0.0009	0.0009	0.0082
85	0.0263	0.0263	0.0263	0.0239
	0.0008	0.0008	0.0008	0.0008
86	0.1196	0.1196	0.1196	-0.0329
	0.0005	0.0005	0.0005	0.0060
87	0.4162	0.6755	0.4162	0.0847
	0.0007	0.0001	0.0007	0.0047
88	0.0121	0.0121	0.0121	-0.0185
	0.0007	0.0007	0.0007	0.0015
89	0.0958	0.0958	0.0958	0.0546
	0.0011	0.0011	0.0011	0.0028
90	0.0853	0.0853	0.0853	-0.0037
	0.0012	0.0012	0.0012	0.0051
91	-0.0142	-0.0142	-0.0142	-0.0379
	0.0004	0.0004	0.0004	0.0012
92	0.1009	0.1009	0.1009	-0.0276
	0.0012	0.0012	0.0012	0.0045
93	0.0604	0.0604	0.0604	-0.0450
	0.0013	0.0013	0.0013	0.0017
94	0.0227	0.0227	0.0227	0.0369
	0.0002	0.0002	0.0002	0.00081
95	0.0598	0.0598	0.0598	-0.0491
	0.0013	0.0013	0.0013	0.0043

Table 4.8 Continued

Intercept/ Slope	Accepted			Reverse
Amino Acid	Ancestral Change	Human Change	Rabbit Change	Change
96	0.0239	0.0239	0.0239	-0.0081
	0.0006	0.0006	0.0006	0.0018
97	0.1635	0.1635	0.1635	0.1170
	0.0012	0.0012	0.0012	0.00351
98	-0.0031	-0.0031	-0.0031	-0.0031
	0.0001	0.0001	0.0001	0.00018
99	0.0698	0.0699	0.0699	-0.0258
	0.0012	0.0012	0.0012	0.0044
100	0.1185	0.1185	0.1185	-0.0490
	0.0004	0.0004	0.0004	0.0056
101	0.1067	0.1067	0.1067	0.0462
	0.0013	0.0013	0.0013	0.0029
102	0.0747	0.0747	0.0747	0.0130
	0.0011	0.0011	0.0011	0.0039
103	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
104	0.7410	0.3444	0.3444	0.0753
	0.0004	0.0005	0.0005	0.0015
105	-0.0045	-0.0045	-0.0045	-0.03160
	0.0006	0.0006	0.0006	0.0011
106	-0.0142	-0.0142	-0.0142	-0.0308
	0.0012	0.0012	0.0012	0.0014
107	0.0721	0.0721	0.0721	-0.0129
	0.0012	0.0012	0.0012	0.0036
108	0.1210	0.1210	0.1210	0.0439
	0.0013	0.0013	0.0013	0.0039
109	0.0681	0.0681	0.0681	0.0748
	0.0013	0.0013	0.0013	0.0013
110	0.0090	0.0090	0.0090	-0.0115
	0.0007	0.0007	0.0007	0.0015
111	-0.0031	-0.0031	-0.0031	-0.0091
	0.0001	0.0001	0.0001	0.0002
112	0.3921	0.6656	0.3921	0.0597
	0.0008	0.0000	0.0008	0.0009
113	0.0322	0.0322	0.0322	0.0325
	0.0012	0.0012	0.0012	0.0013
114	0.1032	0.1032	0.1032	0.0650
	0.0011	0.0011	0.0011	0.0019
115	0.3327	0.3327	0.6867	0.0347
	0.0001	0.0001	0.0003	0.0005
116	0.3263	0.3333	0.3333	0.0070
	0.0000	0.0000	0.0000	0.0000
117	0.0406	0.0406	0.0406	0.0227
	0.0011	0.0011	0.0011	0.0013
118	0.0467	0.0467	0.0467	0.0347
	0.0011	0.0011	0.0011	0.0015

Table 4.8 Continued

Intercept/ Slope Amino Acid	Ancestral Change	Accepted Human Change	Rabbit Change	Reverse Change
119	0.0201	0.0201	0.0201	-0.0127
	0.0005	0.0005	0.0005	0.0013
120	0.0052	0.0052	0.0052	0.0027
	0.0005	0.0005	0.0005	0.0005
121	0.0817	0.0817	0.0817	0.0076
	0.0011	0.0011	0.0011	0.0028
122	0.0102	0.0102	0.0102	-0.0972
	0.0006	0.0006	0.0006	0.0027
123	0.0776	0.0776	0.0776	0.0034
	0.0012	0.0012	0.0012	0.0044
124	0.1779	0.1779	0.1779	0.1586
	0.0012	0.0012	0.0012	0.0037
125	0.7112	0.7073	0.6611	0.0811
	0.0004	0.0004	0.0001	0.0024
126	-0.0095	-0.0095	-0.0095	0.0006
	0.0006	0.0006	0.0006	0.0010
127	0.1023	0.1023	0.1023	0.0283
	0.0013	0.0013	0.0013	0.0039
128	0.1918	0.1918	0.1918	0.0872
	0.0010	0.0010	0.0010	0.0036
129	0.0812	0.0812	0.0812	0.0099
	0.0013	0.0013	0.0013	0.0038
130	0.6646	0.3292	0.3292	-0.0061
	0.0000	0.0001	0.0001	0.001
131	0.0887	0.0887	0.0887	0.0493
	0.0011	0.0011	0.0011	0.0028
132	0.0036	0.0036	0.0036	-0.0747
	0.0009	0.0009	0.0009	0.0025
133	0.0563	0.0563	0.0563	0.0562
	0.0007	0.0007	0.0007	0.0010
134	0.0000	0.0000	0.0000	No Repeats
	0.0000	0.0000	0.0000	
135	0.0611	0.0611	0.0611	0.0250
	0.0011	0.0011	0.0011	0.0020
136	0.0552	0.0552	0.0552	0.0310
	0.0007	0.0007	0.0007	0.0017
137	-0.0034	-0.0034	1.0034	-0.1809
	0.0007	0.0007	0.0007	0.0049
138	0.1073	0.1073	0.1073	-0.0088
	0.0006	0.0006	0.0006	0.0054
139	0.0983	0.0983	0.0983	0.1021
	0.0012	0.0012	0.0012	0.0016
140	0.0708	0.0708	0.0708	-0.0263
	0.0012	0.0012	0.0012	0.0035
141	0.0703	0.0703	0.0703	0.0630
	0.0007	0.0007	0.0007	0.0008

Table 4.8 Continued

Intercept/ Slope Amino Acid	Accepted Ancestral Change	Human Change	Rabbit Change	Reverse Change
142	-0.0006	-0.0006	-0.0006	-0.0118
	0.0001	0.0001	0.0001	0.0004
143	0.0222	0.0222	0.0222	0.0010
	0.0002	0.0002	0.0002	0.0005
144	0.1261	0.1261	0.1261	0.0725
	0.0012	0.0012	0.0012	0.0030
145	0.0794	0.0794	0.0794	0.0323
	0.0013	0.0013	0.0013	0.0027
146	0.0071	0.0071	0.0071	-0.0413
	0.0009	0.0009	0.0009	0.0020

Table 4.9 shows the number of amino acid residues that remain the same as the starting hemoglobin.

Table 4.9
Hemoglobin Similarity

	Number of amino acids similar to:					
Starting	Ancestral		Rabbit		Human	
Hemoglobin	Intercept	Slope	Intercept	Slope	Intercept	Slope
Ancestra	135.7737	-.1239	118.4503	-.1057	119.3220	-.1071
Rabbit	118.1745	-.1075	136.0249	-.1208	123.2636	-.1078
Human	119.1841	-.1083	123.5119	-.1077	136.0913	-.1202
Combined	124.3775	-.1132	125.9957	-.1114	126.2256	-.1117

Table 4.10 takes the process one step further by presenting the hemoglobin simularity regression for each of the methods used in this study.

Table 4.10
Hemoglobin Similarity Regression

Intercept/ Slope	Random	Dayhoff	Zuckerkandl	Fitch	Nearest-Neighbor
			Ancestral Starting Hemoglobin		
Ancestral	141.09	131.85	131.95	133.12	140.86
	-.1178	-.1392	-.1268	-.1334	-.1031
Rabbit	122.85	114.99	115.28	116.08	123.05
	-.1002	-.1181	-.1098	-.1137	-.0869
Human	123.83	115.78	116.23	116.90	123.88
	-.1015	-.1189	-.1103	-.1155	-.0893
			Rabbit Starting Hemoglobin		
Ancestral	122.81	114.55	115.03	115.76	122.72
	-.1023	-.1194	-.1114	-.1147	-.0894
Rabbit	141.36	132.04	132.95	133.49	140.79
	-.1139	-.1340	-.1256	-.1137	-.1014
Human	127.79	119.66	120.08	121.08	127.69
	-.1016	-.1204	-.1120	-.1159	-.0892
			Human Starting Hemoglobin		
Ancestral	123.86	115.55	115.96	116.80	123.75
	-.1032	-.1210	-.1110	-.1167	-.0894
Rabbit	127.97	119.90	120.43	121.43	127.83
	-.1008	-.1213	-.1119	-.1165	-.0881
Human	141.27	132.10	132.04	133.56	141.15
	-.1146	-.1341	-.1235	-.1292	-.0991

Table 4.11 presents the final tabular results examined in this effort. The amino acid residues similarity to the starting hemoglobins is used in a regression by iterations for each position of each of the three starting hemoglobins.

Table 4.11
Amino Acid Similarity Regression

Amino Acid	Ancestral		Human		Rabbit	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
1	.9575	-.0009	.9575	-.0009	.9575	-.0009
2	.9474	-.0012	.9474	-.0012	.9474	-.0012
3	.3329	-.0003	.6820	-.0004	.3329	-.0003
4	.6207	-.0008	.6207	-.0008	.3276	-.0000
5	.2685	-.0005	.3081	-.0004	.2497	-.0004
6	.8566	-.0012	.8566	-.0012	.8566	-.0012

Table 4.11 Continued

Amino Acid	Ancestral		Human		Rabbit	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
7	.8475	-.0010	.8475	-.0010	.8475	-.0010
8	.9130	-.0012	.9130	-.0012	.9130	-.0012
9	.3259	-.0002	.6377	-.0001	.6377	-.0001
10	.8845	-.0011	.8845	-.0011	.8845	-.0011
11	.3330	-.0001	.6306	-.0005	.6306	-.0005
12	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
13	.3312	-.0004	.6420	-.0002	.6420	-.0002
14	.9644	-.0005	.9644	-.0005	.9644	-.0005
15	.9365	-.0008	.9365	-.0008	.9365	-.0008
16	.9112	-.0008	.9112	-.0008	.9112	-.0008
17	.9444	-.0011	.9444	-.0011	.9444	-.0011
18	.9830	-.0012	.9830	-.0012	.9830	-.0012
19	.8651	-.0013	.8651	-.0013	.8651	-.0013
20	.9195	-.0010	.9195	-.0010	.9195	-.0010
21	.5692	-.0008	.2635	-.0004	.5692	-.0008
22	1.0031	-.0001	1.0031	-.0001	1.0031	-.0001
23	.8238	-.0010	.8238	-.0010	.8238	-.0010
24	.8941	-.0007	.8941	-.0007	.8941	-.0007
25	.8435	-.0012	.8435	-.0012	.8435	-.0012
26	.8030	-.0010	.8030	-.0010	.8030	-.0010
27	.9238	-.0011	.9238	-.0011	.9238	-.0011
28	.9509	-.0009	.9509	-.0009	.9509	-.0009
29	.8235	-.0011	.8235	-.0011	.8235	-.0011
30	.2721	-.0004	.6260	-.0008	.6260	-.0008
31	.9830	-.0003	.9830	-.0003	.9830	-.0003
32	.9810	-.0007	.9810	-.0007	.9810	-.0007
33	.9830	-.0004	.9830	-.0004	.9830	-.0004
34	.9116	-.0014	.9116	-.0014	.9116	-.0014
35	.9970	-.0001	.9970	-.0001	.9970	-.0001
36	.7840	-.0012	.7840	-.0012	.7840	-.0012
37	.9558	-.0012	.9558	-.0012	.9558	-.0012
38	.9281	-.0010	.9281	-.0010	.9281	-.0010
39	.8206	-.0008	.8206	-.0008	.8206	-.0008
40	.9234	-.0008	.9234	-.0008	.9234	-.0008
41	.9496	-.0007	.9496	-.0007	.9496	-.0007
42	.8543	-.0011	.8543	-.0011	.8543	-.0011
43	.3395	-.0004	.6146	-.0007	.6146	-.0007
44	1.0121	-.0012	1.0121	-.0012	1.0121	-.0012
45	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
46	.9286	-.0009	.9286	-.0009	.9286	-.0009
47	.9628	-.0006	.9628	-.0006	.9628	-.0006
48	1.0121	-.0012	1.0121	-.0012	1.0121	-.0012
49	.9854	-.0000	.9854	-.0000	.9854	-.0000
50	.6667	-.0000	.3333	-.0000	.6667	-.0000
51	.6247	-.0002	.2946	-.0003	.6247	-.0002
52	.6366	-.0002	.6366	-.0002	.2884	-.0004
53	.9194	-.0004	.9194	-.0004	.9194	-.0004
54	.9733	-.0001	.9733	-.0001	.9733	-.0001

Table 4.11 Continued

Amino Acid	Ancestral		Human		Rabbit	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
55	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
56	.5990	-.0007	.5990	-.0007	.3438	-.0001
57	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
58	.9063	-.0010	.9063	-.0010	.9063	-.0010
59	.7966	-.0012	.7966	-.0012	.7966	-.0012
60	.9718	-.0008	.9718	-.0008	.9718	-.0008
61	.9725	-.0009	.9725	-.0009	.9725	-.0009
62	.9177	-.0011	.9177	-.0011	.9177	-.0011
63	.9915	-.0012	.9915	-.0012	.9915	-.0012
64	.8265	-.0012	.8265	-.0012	.8265	-.0012
65	.8558	-.0008	.8558	-.0008	.8558	-.0008
66	.9701	-.0006	.9701	-.0006	.9701	-.0006
67	.8903	-.0012	.8903	-.0012	.8903	-.0012
68	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
69	.6173	-.0008	.6173	-.0008	.3351	-.0001
70	1.0290	-.0012	1.0290	-.0012	1.0290	-.0012
71	.8859	-.0013	.8859	-.0013	.8859	-.0013
72	.3340	-.0002	.6655	-.0001	.6655	-.0001
73	.5582	-.0008	.5582	-.0008	.3788	-.0001
74	.9140	-.0012	.9140	-.0012	.9140	-.0012
75	1.0112	-.0010	1.0112	-.0010	1.0112	-.0010
76	.2940	-.0040	.2991	-.0001	.2907	-.0004
77	.8775	-.0013	.8775	-.0013	.8775	-.0013
78	.9657	-.0004	.9657	-.0004	.9657	-.0004
79	.8073	-.0012	.8073	-.0012	.8073	-.0012
80	.8931	-.0012	.8931	-.0012	.8931	-.0012
81	.9540	-.0006	.9540	-.0006	.9540	-.0006
82	.8131	-.0012	.8131	-.0012	.8131	-.0012
83	.8376	-.0008	.8376	-.0008	.8376	-.0008
84	.8001	-.0009	.8001	-.0009	.8001	-.0009
85	.9737	-.0008	.9737	-.0008	.9737	-.0008
86	.8804	-.0005	.8804	-.0005	.8804	-.0005
87	.5838	-.0007	.3245	-.0001	.5838	-.0007
88	.9879	-.0007	.9879	-.0007	.9879	-.0007
89	.9042	-.0011	.9042	-.0011	.9042	-.0011
90	.9147	-.0012	.9147	-.0012	.9147	-.0012
91	1.0142	-.0004	1.0142	-.0004	1.0142	-.0004
92	.8991	-.0012	.8991	-.0012	.8991	-.0012
93	.9396	-.0013	.9396	-.0013	.9396	-.0013
94	.9773	-.0002	.9773	-.0002	.9773	-.0002
95	.9402	-.0013	.9402	-.0013	.9402	-.0013
96	.9761	-.0006	.9761	-.0006	.9761	-.0006
97	.8365	-.0012	.8365	-.0012	.8365	-.0012
98	1.0031	-.0001	1.0031	-.0001	1.0031	-.0001
99	.9302	-.0012	.9301	-.0012	.9301	-.0012
100	.8815	-.0004	.8815	-.0004	.8815	-.0004
101	.8933	-.0013	.8933	-.0013	.8933	-.0013
102	.9253	-.0011	.9253	-.0011	.9253	-.0011

Table 4.11 Continued

Amino	Ancestral		Human		Rabbit	
Acid	Intercept	Slope	Intercept	Slope	Intercept	Slope
103	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
104	.2590	-.0004	.6556	-.0005	.6556	-.0005
105	1.0045	-.0006	1.0045	-.0006	1.0045	-.0006
106	1.0142	-.0012	1.0142	-.0012	1.0142	-.0012
107	.9279	-.0012	.9279	-.0012	.9279	-.0012
108	.8790	-.0013	.8790	-.0013	.8790	-.0013
109	.9319	-.0013	.9319	-.0013	.9319	-.0013
110	.9910	-.0007	.9910	-.0007	.9910	-.0007
111	1.0031	-.0001	1.0031	-.0001	1.0031	-.0001
112	.6079	-.0008	.3344	-.0000	.6079	-.0008
113	.9678	-.0012	.9678	-.0012	.9678	-.0012
114	.8968	-.0011	.8968	-.0011	.8968	-.0011
115	.6673	-.0001	.6673	-.0001	.3133	-.0003
116	.3263	-.0000	.6667	-.0000	.6667	-.0000
117	.9594	-.0011	.9594	-.0011	.9594	-.0011
118	.9532	-.0011	.9532	-.0011	.9532	-.0011
119	.9799	-.0005	.9799	-.0005	.9799	-.0005
120	.9948	-.0005	.9948	-.0005	.9948	-.0005
121	.9183	-.0011	.9183	-.0011	.9183	-.0011
122	.9898	-.0006	.9898	-.0006	.9898	-.0006
123	.9224	-.0012	.9224	-.0012	.9224	-.0012
124	.8221	-.0012	.8221	-.0012	.8221	-.0012
125	.2888	-.0004	.2922	-.0004	.3389	-.0001
126	1.0095	-.0006	1.0095	-.0006	1.0095	-.0006
127	.8977	-.0013	.8977	-.0013	.8977	-.0013
128	.8082	-.0010	.8082	-.0010	.8082	-.0010
129	.9188	-.0013	.9188	-.0013	.9188	-.0013
130	.3354	-.0000	.6708	-.0001	.6708	-.0001
131	.9113	-.0011	.9113	-.0011	.9113	-.0011
132	.9964	-.0009	.9964	-.0009	.9964	-.0009
133	.9437	-.0007	.9437	-.0007	.9437	-.0007
134	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
135	.9389	-.0011	.9389	-.0011	.9389	-.0011
136	.9448	-.0007	.9448	-.0007	.9448	-.0007
137	1.0034	-.0007	1.0034	-.0007	1.0034	-.0007
138	.8927	-.0006	.8927	-.0006	.8927	-.0006
139	.9017	-.0012	.9017	-.0012	.9017	-.0012
140	.9292	-.0012	.9292	-.0012	.9292	-.0012
141	.9297	-.0007	.9297	-.0007	.9297	-.0007
142	1.0006	-.0001	1.0006	-.0001	1.0006	-.0001
143	.9778	-.0002	.9778	-.0002	.9778	-.0002
144	.8739	-.0012	.8739	-.0012	.8739	-.0012
145	.9206	-.0013	.9206	-.0013	.9206	-.0013
146	.9919	-.0009	.9919	-.0009	.9919	-.0009

CHAPTER V

CONCLUSIONS

The generalizability of results from this work is restricted due to the limited availability of sequence data for protein generating sequences. The DNA sequencing data for human alpha, beta, and sigma hemoglobin; for mouse alpha and beta hemoglobin; and for rabbit alpha and sigma hemoglobin is currently known. Until the sequencing data from a wide variety of different proteins from a large cross-section of different species, the full implication of the use of these techniques will be difficult to completely evaluate.

The review of the literature revealed a great deal of literature relative to the possible shemes for the evolution of DNA. Literature from basic fields of study have not yet converged. Literature being produced in the field of population genetics have addressed the dynamics of phenotypic introduction and propogation of mutations in the genetic material of the organism. The general results from the work in the field to date is that mutations resulting in neutral, or nearly neutral advantage to the survival of an organism in the environment are not supportable from the frequency of mutations observed when compared to the best

models of the rate of acceptance of this type of mutation. This effort found in almost all cases an order of magnitude higher rejection than acceptance, even using the extremely lax criteria used in this effort for acceptance.

The molecular biologists have found evidence for several effects that suggest that many of the mutations that are expected to be found in the primary sequence of amino acids in protein should result in selectively neutral mutations. Further, studies which relate the differences in the primary sequence of proteins such as hemoglobin, cytochrome c, and fibrinogin suggest a constant rate of amino acid replacement for each protein which provides evolutionary relationships between species which agrees well with the phylogenic relationships that have been previously established. This strongly suggests that neutral mutations would be expected to be the primary mechanism envolved. Some of the assumptions used for estimating the transition probabilities of amino acid may be suspect. Use of the nucleotides sequences instead of the amino acid sequences as the methodology adapted in this effort should avoid these same difficulties and was the motivating force for the selection ofthe modeling techniquechosen in this effort.

Information theory and the application of information theory have been applied to information on the evolutionary system. Involvement of this field to the problems existing in the genetic system have not had a large impact to da_e.

The genetic code and the reduncies of the system have been successfully evaluated. Application to the mutation of amino acid sequences have not provided significant insight into the behavior of the system. More basic information provided from nucleotide mutation behavior should allow further analysis in this area with a better prospect for success. Recent information that has been obtained in studies of the chemical and physical characteristics of the nucleic acid found in organisms has changed many ideas about possible interactions that may be occurring. The observation of multiple repeated sequences of nucleotides in the DNA of eukaryotes and the finding of intervening sequences within the gene that codes for DNA will have to be understood and incorporated into future work.

Also, the field of chemical physics has yielded information on chain stability caused by the ratio of guanine and cytosine and the stabilization of mRNA by the formation of autocomplementary regions and the formation of loops offer potential for understanding the selective advantage of nucleotide changes that result in amino acid point mutations which do not appear to have selective advantage when examined on the basis of protein function.

The fields of study involved in trying to understand the underlying mechanisms does not appear to have been incorporated into a systematic framework necessary for the evaluation of system performance. This thesis effort is

an attempt to try to evaluate the system by examining the output produced by several different sets of inputs with different methods of modeling system performance, since the underlying mechanisms were uncharacterized. Estimates of the transition probabilites were obtained from three different sources as well as assumed to be completely random. The output of the system was characterized at the nucleotide level and at the level of the amino acid. The output of the system was "locked" in place by constraining the acceptable amino acids at each position of the chain to those residues that have been characterized in previous studies. This artificial constraint was an attempt to restrict the model to a domain that would be evolutionary significant. In other words, this was a primative attempt to collectively model the possibility or random mutation resulting in selective advantage at the nucleotide and the amino acid level. As a better understanding of mechanisms that have physical significance is formulated, more detailed modeling of the process will be possible.

There were several interesting observations that can be made regarding the results of the modeling effort. All of the transition frequency were based upon estimates of an accepted amino acid change in 10,000,000 years for a protein 140 residues long. The data in table 4.6 reflects that using the Dayhoff transition frequencies resulted in the highest acceptance of new amino acid residues while the

nearest-neighbor transition frequencies resulted in the lowest acceptance rate. The random data was nearly identical with the nearest-neighbor rate. All three simple transition methodologies, Dayhoff, Zuckerkandl, and Fitch were very close to having the same rate of accepting a mutation. The rate at which a previous amino acid residue was back mutated to a residue that was already at the same position was very high and uniform across methods. 99% of all accepted mutations using the random transition probabilities resulted in a back mutation. 97%, 96%, and 95% were the respective back mutation rate for Dayhoff, Zuckerkandl, and Fitch. Nearest-neighbor back mutations accounted for 93% of the accepted mutations. This extremely high percentage of back mutations at the amino acid level was not expected before this analysis was begun. Table 4.4 for the nucleotide transition regression sheds some light on the situation. All five methods resulted in the acceptance of only 15% to 16% of the nucleotide changes. Of the nucleotide changes that did occur, 17%, 44%, 42%, 42%, and 19% of the changes were backmutations. The rates of transition are nearly the same for allowing nucleotide changes as for accepting amino acid changes. At first thought, it would appear that some form of the wobble hypothesis of Crick might provide the answer. The wobble hypothesis has been applied to the degenerate pairing of the third nucleotide of mRNA to tRNA in a manner which preserves

the reliability of obtaining the same amino acid in the peptide chain. When the data from table 4.7 is examined, no significant trend of either allowing, repeating, or rejecting nucleotide based upon the position in the codon can be found to support a wobble relationship in the mutations at the DNA level. Upon further investigation, the relationship between nucleotide transition frequency and amino acid transition frequency are tied in two cycles. The amino acids acceptable at any particular position typically form a small subset of the 20 residues possible. As a result, nucleotides changes are allowed at any of the positions in the codon with few restrictions, but after a very few resulting changes in amino acids, they begin repeating. The repetive cycling of amino acids was much higher than anticipated by any of the literature. Most of the literature dealing with the evolutionary fixation of mutations in amino acids did not reflect the high degree of repetition that was found to exist at the amino acid level.

Interestingly enough, the method used in the simulation proved to be the driver for the type of repetition seen. The repetition cycles were very dependent on the position. At one end of the spectrum was the use of the random method. Most of the repeats observed were simple back mutations at the third position in the DNA codon. As the transitions of the nucleotides is more controlled such as in the nearest-neighbor approach, repeats of amino acids occur more often

only after cycles of two, three, or somtimes even more changes in the amino acid residue. These cycles are found to regularly repeat. The structured transition probabilities of the three methods seemed to be intermediate in behavior. Some two and three cycle transition patterns were seen, but they were not regularily repeated as were the transitions observed with the nearest-neighbor method.

This difference in mutational patterns depending on the non-random transition probabilities seems to paint a different picture of the process of evolution. The fixation of a point mutation may be part of an equillibrium searching mechanism important in the survival of the organism. The strength of the Ising model used with the nearest-neighbor transition probabilities and the allowable amino acid replacements may enable the organism to control random genetic drift and neutral mutations at the protein level to control the stability of the DNA and the RNA chains. The ability to control the guanine-cytosine content of DNA is important in the information potential of DNA. It is also important in the stablity of the chain to denaturalization from heat as well as ion levels. It controls the rate of chain separation. These physical properties of the DNA chain have been shown to follow the same behavior and performance as would be expected from an Ising model.

Much further work needs to be done. Further identification of more DNA from more species and for

different proteins needs to be conducted. With a larger database, more closure on the process of evolution may be examined. DNA from species of very distant, or non-existant, connection to the environment would be instrumental in identifying several points. An opportunity to use DNA sequences from species found around the hydrogen sulfide vents on the ocean floor in the Atlantic and the Pacific oceans has high potential to shed light on many of the theories existing in the field of evolutionary biology.

APPENDIX

APPENDIX A

PROGRAM SOURCE LISTING

PROGRAM SOURCE LISTING

```
00005      PROGRAM (COMPUTERANDOM MUTATIONS FOR BETA Hb)
00010        INTEGER E,F,K
00020        DIMENSION NA(438,50),MA(146,50)
00030        DIMENSION NULL(438),PCT(438)
00040        DIMENSION NCOUNT(4,4),MCOUNT(28,28)
00050        DIMENSION MCRIT(146,14)
00060        DIMENSION MGC(16,4),N(450),M(150),NP(450,4),
00061       1MP(150,4)
00070        DIMENSION T(64,3)
00080        DIMENSION NR(438),MR(150),MCH(150),MCR(150),
00081       1MCA(150)
00090        IXS=9636
00110        CALL HB(NP)
00120        CALL GC(MGC)
00130        CALL INIT1(NP,MP,MGC)
00190        CALL AAAR(MCRIT)
00191        DO 1001 INTE=1,3
00192        IF (INTE.EQ.1) INTER=700
00193        IF (INTE.EQ.2) INTER=40
00194        IF (INTE.EQ.3) INTER=6
00200        CALL INIT(IX,IXS,F,E,N,INTER,NCOUNT,MCOUNT,NULL,
00210       1NA,MA,M,MGC,NP,NIP,NR,MR,MP,IH,MCH,MCR,MCA)
00220        DO 10 L=1,INTER
00230        DO 20 I=2,438
00240        CALL TRAN1(NUC,I,INTER,N,IX)
00250        IF (NUC.EQ.N(I))  GO TO 20
00260        CALL MUTATE(I,MCRIT,NULL,NUC,NCOUNT,MCOUNT,NA,
00270       1MA,N,M,MGC,E,F,NR,MR)
00280     20 CONTINUE
00290     10 CONTINUE
00300        PRINT 2
00310        METH=1
00320        CALL OUT(M,N,NA,MA,NULL,MCOUNT,NCOUNT,IH,IXS,
00330       1METH,INTER,NR,MR,MCH,MCR,MCA,MP)
00340        DO 30 K=1,3
00350        CALL INIT(IX,IXS,F,E,N,INTER,NCOUNT,MCOUNT,NULL,
00360       1NA,MA,M,MGC,NP,NIP,NR,MR,MP,IH,MCH,MCR,MCA)
00370        DO 40 L=1,INTER
00380        DO 50 I=2,438
00390        CALL TRAN2(NUC,I,INTER,N,K,IX)
00400        IF (NUC.EQ.(N(I))) GO TO 50
00410        CALL MUTATE(I,MCRIT,NULL,NUC,NCOUNT,MCOUNT,NA,
00420       1MA,N,M,MGC,E,F,NR,MR)
00430     50 CONTINUE
00440     40 CONTINUE
00450        IF (K.EQ.1)  PRINT 3
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00460        IF (K.EQ.1)  METH=2
00470        IF (K.EQ.2)  PRINT 4
00480        IF (K.EQ.2)  METH=3
00490        IF (K.EQ.3)  PRINT 5
00500        IF (K.EQ.3)  METH=4
00510 C      CALL RESULT(M,N,NA,MA,NULL,MCOUNT,NCOUNT)
00520        CALL OUT(M,N,NA,MA,NULL,MCOUNT,NCOUNT,IH,IXS,
00530       1METH,INTER,NR,MR,MCH,MCR,MCA,MP)
00540     30 CONTINUE
00550        CALL INIT(IX,IXS,F,E,N,INTER,NCOUNT,MCOUNT,NULL,
00560       1NA,MA,M,MGC,NP,NIP,NR,MR,MP,IH,MCH,MCR,MCA)
00570        CALL TP(T)
00580        DO 60 L=1,INTER
00590        DO 70 I=2,438
00600        CALL TRAN3(NUC,I,INTER,N,T,IX)
00610        IF (NUC.EQ.(N(I))) GO TO 70
00620        CALL MUTATE(I,MCRIT,NULL,NUC,NCOUNT,MCOUNT,NA,
00630       1MA,N,M,MGC,E,F,NR,MR)
00640     70 CONTINUE
00650     60 CONTINUE
00660        PRINT 6
00670        METH=5
00680 C      CALL RESULT(M,N,NA,MA,NULL,MCOUNT,NCOUNT)
00690        CALL OUT(M,N,NA,MA,NULL,MCOUNT,NCOUNT,IH,IXS,
00700       1METH,INTER,NR,MR,MCH,MCR,MCA,MP)
00710   1001 CONTINUE
00715   1000 CONTINUE
00750      2 FORMAT (16H0RANDUM MUTATION)
00760      3 FORMAT (42H0NUCLEOTIDE DEPENDENT MUTATION-
00761       1ZUKERKANDL)
00770      4 FORMAT (36H0NUCLEOTIDE DEPENDENT MUTATION-FITCH)
00780      5 FORMAT (38H0NUCLEOTIDE DEPENDENT MUTATION-
00781       1DAYHOFF)
00790      6 FORMAT (36H0NEAREST NEIGHBOR DEPENDENT MUTATION)
00810        STOP
00820        END
10010        SUBROUTINE HB(NP)
10020        DIMENSION NP(450,4)
10030        DO 10 I=1,450
10040        NP(I,1)=0
10050        NP(I,2)=0
10060        NP(I,3)=0
10070     10 CONTINUE
10110        NP(436,1)=2
10120        NP(437,1)=1
10130        NP(438,1)=2
10140        NP(433,1)=3
10141        NP(433,2)=1
10142        NP(433,3)=1
10150        NP(434,1)=4
10160        NP(435,1)=3
10169        NP(430,1)=2
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10170        NP(431,1)=1
10180        NP(432,1)=3
10181        NP(432,2)=2
10182        NP(432,3)=2
10190        NP(427,1)=1
10200        NP(428,1)=3
10210        NP(429,1)=4
10220        NP(424,1)=1
10230        NP(425,1)=3
10231        NP(425,2)=2
10240        NP(426,1)=3
10241        NP(426,2)=4
10242        NP(426,3)=2
10250        NP(421,1)=2
10260        NP(422,1)=4
10270        NP(423,1)=2
10280        NP(418,1)=2
10290        NP(419,1)=4
10300        NP(420,1)=2
10310        NP(415,1)=2
10320        NP(416,1)=4
10330        NP(417,1)=4
10340        NP(412,1)=1
10350        NP(413,1)=3
10360        NP(414,1)=1
10362        NP(414,3)=2
10370        NP(409,1)=2
10380        NP(410,1)=3
10390        NP(411,1)=2
10400        NP(406,1)=1
10401        NP(406,2)=3
10410        NP(407,1)=1
10420        NP(408,1)=2
10422        NP(408,3)=4
10430        NP(403,1)=1
10440        NP(404,1)=3
10450        NP(405,1)=4
10460        NP(400,1)=3
10470        NP(401,1)=3
10480        NP(402,1)=2
10482        NP(402,3)=1
10490        NP(397,1)=2
10500        NP(398,1)=1
10510        NP(399,1)=3
10520        NP(394,1)=2
10530        NP(395,1)=2
10540        NP(396,1)=1
10550        NP(391,1)=3
10560        NP(392,1)=2
10570        NP(393,1)=2
10580        NP(388,1)=2
10590        NP(389,1)=4
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10600         NP(390,1)=4
10610         NP(385,1)=2
10620         NP(386,1)=1
10630         NP(387,1)=2
10640         NP(382,1)=3
10641         NP(382,2)=1
10642         NP(382,3)=1
10650         NP(383,1)=4
10660         NP(384,1)=4
10670         NP(379,1)=2
10680         NP(380,1)=1
10690         NP(381,1)=2
10700         NP(376,1)=1
10701         NP(376,2)=4
10702         NP(376,3)=4
10710         NP(377,1)=4
10720         NP(378,1)=2
10730         NP(373,1)=4
10740         NP(374,1)=4
10750         NP(375,1)=2
10760         NP(370,1)=1
10770         NP(371,1)=1
10780         NP(372,1)=2
10790         NP(367,1)=1
10800         NP(368,1)=2
10810         NP(369,1)=2
10820         NP(364,1)=1
10830         NP(365,1)=2
10840         NP(366,1)=2
10850         NP(361,1)=2
10860         NP(362,1)=4
10870         NP(363,1)=2
10880         NP(358,1)=3
10890         NP.359,1)=3
10900         NP(360,1)=2
10910         NP(355,1)=2
10920         NP(356,1)=1
10930         NP(357,1)=3
10940         NP(352,1)=3
10950         NP(353,1)=2
10960         NP(354,1)=2
10970         NP(349,1)=2
10980         NP(350,1)=1
10981         NP(350,2)=2
10990         NP(351,1)=4
11000         NP(346,1)=2
11010         NP(347,1)=1
11020         NP(348,1)=3
11030         NP(343,1)=2
11040         NP(344,1)=1
11050         NP(345,1)=3
11060         NP(340,1)=2
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11061        NP(340,2)=1
11062        NP(340,3)=1
11070        NP(341,1)=1
11080        NP(342,1)=2
11090        NP(337,1)=3
11100        NP(338,1)=1
11110        NP(339,1)=2
11120        NP(334,1)=3
11130        NP(335,1)=4
11140        NP(336,1)=1
11150        NP(331,1)=1
11160        NP(332,1)=3
11170        NP(333,1)=3
11180        NP(328,1)=2
11190        NP(329,1)=2
11200        NP(330,1)=1
11210        NP(325,1)=3
11220        NP(326,1)=3
11230        NP(327,1)=4
11240        NP(322,1)=2
11250        NP(323,1)=4
11260        NP(324,1)=3
11270        NP(319,1)=2
11280        NP(320,1)=2
11290        NP(321,1)=4
11300        NP(316,1)=3
11310        NP(317,1)=1
11320        NP(318,1)=1
11330        NP(313,1)=1
11331        NP(313,2)=3
11340        NP(314,1)=1
11350        NP(315,1)=1
11360        NP(310,1)=2
11362        NP(310,3)=3
11370        NP(311,1)=4
11380        NP(312,1)=2
11390        NP(307,1)=3
11400        NP(308,1)=3
11410        NP(309,1)=1
11420        NP(304,1)=1
11430        NP(305,1)=1
11440        NP(306,1)=1
11450        NP(301,1)=2
11460        NP(302,1)=2
11470        NP(303,1)=2
11480        NP(298,1)=1
11481        NP(298,2)=3
11490        NP(299,1)=4
11500        NP(300,1)=2
11510        NP(295,1)=2
11520        NP(296,1)=1
11530        NP(297,1)=3
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11550        NP(293,1)=3
11560        NP(294,1)=1
11570        NP(289,1)=1
11580        NP(290,1)=3
11590        NP(291,1)=4
11591        NP(291,2)=1
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11600        NP(286,1)=1
11601        NP(286,2)=4
11610        NP(287,1)=3
11620        NP(288,1)=3
11621        NP(288,2)=2
11622        NP(288,3)=2
11630        NP(283,1)=1
11640        NP(284,1)=4
11650        NP(285,1)=2
11651        NP(285,2)=4
11660        NP(280,1)=4
11670        NP(281,1)=3
11680        NP(282,1)=2
11690        NP(277,1)=1
11700        NP(278,1)=1
11710        NP(279,1)=2
11720        NP(274,1)=2
11730        NP(275,1)=1
11740        NP(276,1)=4
11750        NP(271,1)=3
11760        NP(272,1)=2
11761        NP(272,2)=4
11770        NP(273,1)=2
11771        NP(273,2)=4
11780        NP(268,1)=3
11781        NP(268,2)=
11782        NP(268,3)=1
11790        NP(269,1)=4
11800        NP(270,1)=4
11810        NP(265,1)=1
11820        NP(266,1)=3
11830        NP(267,1)=3
11840        NP(262,1)=2
11850        NP(263,1)=4
11860        NP(264,1)=4
11870        NP(259,1)=2
11880        NP(260,1)=1
11890        NP(261,1)=2
11900        NP(256,1)=2
11910        NP(257,1)=4
11920        NP(258,1)=4
11930        NP(253,1)=1
11940        NP(254,1)=3
11950        NP(255,1)=2
```
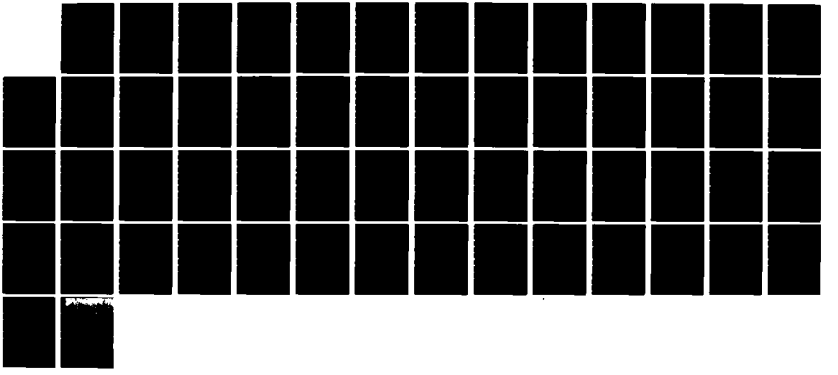
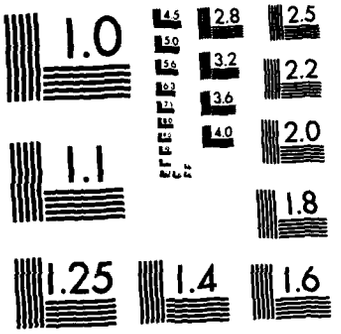

AD-A134 408 THE SIMULATION AND ANALYSIS OF AN EVOLUTIONARY MODEL OF 2/2
DEOXYRIBONUCLEIC ACID (DNA)(U) AIR FORCE INST OF TECH
WRIGHT-PATTERSON AFB OH SCHOOL OF SYST.. R E MCNALLY
UNCLASSIFIED SEP 83 AFIT-LSSR-87-80 F/G 12/1 NL





MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

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11990         NP(247,1)=3
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12110         NP(249,1)=2
12020         NP(244,1)=2
12030         NP(245,1)=4
12040         NP(246,1)=4
12050         NP(241,1)=4
12051         NP(241,2)=2
12060         NP(242,1)=4
12070         NP(243,1)=4
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12100         NP(240,1)=2
12110         NP(235,1)=3
12111         NP(235,2)=2
12112         NP(235,3)=2
12120         NP(236,1)=1
12130         NP(237,1)=3
12140         NP(232,1)=1
12150         NP(233,1)=2
12151         NP(233,2)=3
12160         NP(234,1)=2
12170         NP(229,1)=3
12180         NP(230,1)=3
12190         NP(231,1)=2
12200         NP(226,1)=1
12210         NP(227,1)=1
12211         NP(227,2)=3
12220         NP(228,1)=1
12230         NP(223,1)=1
12240         NP(224,1)=2
12250         NP(225,1)=4
12252         NP(225,3)=2
12260         NP(220,1)=1
12261         NP(220,2)=2
12270         NP(221,1)=4
12280         NP(222,1)=2
12290         NP(217,1)=3
12291         NP(217,2)=1
12292         NP(217,3)=1
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12310         NP(219,1)=2
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12360         NP(212,1)=3
12361         NP(212,2)=2
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12370        NP(213,1)=2
12371        NP(213,2)=4
12372        NP(213,3)=4
12380        NP(208,1)=3
12390        NP(209,1)=4
12400        NP(210,1)=3
12410        NP(205,1)=2
12420        NP(206,1)=1
12430        NP(207,1)=3
12440        NP(202,1)=3
12450        NP(203,1)=4
12460        NP(204,1)=2
12470        NP(199,1)=3
12480        NP(200,1)=4
12490        NP(201,1)=4
12500        NP(196,1)=3
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12530        NP(193,1)=2
12531        NP(193,2)=4
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12580        NP(192,1)=2
12590        NP(187,1)=3
12600        NP(188,1)=3
12610        NP(189,1)=4
12620        NP(184,1)=1
12630        NP(185,1)=1
12640        NP(186,1)=1
12650        NP(181,1)=3
12651        NP(181,2)=1
12652        NP(181,3)=1
12660        NP(182,1)=3
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12680        NP(178,1)=4
12681        NP(178,2)=2
12690        NP(179,1)=3
12691        NP(179,2)=4
12692        NP(179,3)=4
12700        NP(180,1)=4
12710        NP(175,1)=2
12720        NP(176,1)=1
12730        NP(177,1)=3
12740        NP(172,1)=1
12750        NP(173,1)=2
12760        NP(174,1)=4
12770        NP(169,1)=2
12771        NP(169,2)=4
```

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12772         NP(169,3)=4
12780         NP(170,1)=4
12790         NP(171,1)=2
12800         NP(166,1)=2
12810         NP(167,1)=1
12820         NP(168,1)=3
12830         NP(163,1)=3
12840         NP(164,1)=4
12850         NP(165,1)=3
12860         NP(160,1)=1
12870         NP(161,1)=2
12880         NP(162,1)=1
12890         NP(157,1)=3
12900         NP(158,1)=4
12910         NP(159,1)=2
12920         NP(154,1)=2
12930         NP(155,1)=4
12940         NP(156,1)=4
12950         NP(151,1)=2
12960         NP(152,1)=1
12970         NP(153,1)=3
12980         NP(148,1)=3
12990         NP(149,1)=4
13000         NP(150,1)=3
13010         NP(145,1)=2
13020         NP(146,1)=1
13030         NP(147,1)=2
13040         NP(142,1)=1
13050         NP(143,1)=4
13060         NP(144,1)=2
13070         NP(139,1)=1
13080         NP(140,1)=3
13090         NP(141,1)=3
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13110         NP(137,1)=4
13120         NP(138,1)=2
13130         NP(133,1)=3
13140         NP(134,1)=4
13150         NP(135,1)=4
13160         NP(130,1)=3
13170         NP(131,1)=1
13180         NP(132,1)=1
13190         NP(127,1)=2
13200         NP(128,1)=2
13202         NP(128,3)=4
13210         NP(129,1)=4
13220         NP(124,1)=3
13230         NP(125,1)=1
13240         NP(126,1)=3
13250         NP(121,1)=2
13260         NP(122,1)=1
13270         NP(123,1)=3
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13280        NP(118,1)=3
13290        NP(119,1)=2
13300        NP(120,1)=2
13310        NP(115,1)=3
13320        NP(116,1)=4
13330        NP(117,1)=4
13340        NP(112,1)=2
13350        NP(113,1)=1
13360        NP(114,1)=2
13370        NP(109,1)=2
13380        NP(110,1)=1
13390        NP(111,1)=3
13400        NP(106,1)=3
13401        NP(106,2)=1
13402        NP(106,3)=1
13410        NP(107,1)=1
13420        NP(108,1)=2
13430        NP(103,1)=1
13440        NP(104,1)=2
13441        NP(104,2)=1
13442        NP(104,3)=1
13450        NP(105,1)=1
13451        NP(105,2)=4
13452        NP(105,3)=4
13460        NP(100,1)=2
13470        NP(101,1)=1
13480        NP(102,1)=2
13490        NP(97,1)=2
13500        NP(98,1)=1
13510        NP(99,1)=3
13520        NP(94,1)=3
13521        NP(94,2)=1
13522        NP(94,3)=1
13530        NP(95,1)=3
13531        NP(95,2)=2
13540        NP(96,1)=2
13550        NP(91,1)=1
13560        NP(92,1)=4
13562        NP(92,3)=2
13570        NP(93,1)=3
13580        NP(88,1)=3
13581        NP(88,2)=1
13582        NP(88,3)=1
13590        NP(89,1)=4
13600        NP(90,1)=3
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13640        NP(82,1)=3
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13670        NP(79,1)=4
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13690        NP(81,1)=4
13700        NP(76,1)=4
13710        NP(77,1)=4
13720        NP(78,1)=2
13730        NP(73,1)=3
13740        NP(74,1)=1
13750        NP(75,1)=1
13760        NP(70,1)=3
13761        NP(70,2)=1
13762        NP(70,3)=1
13770        NP(71,1)=3
13780        NP(72,1)=4
13790        NP(67,1)=4
13791        NP(67,2)=1
13792        NP(67,3)=1
13800        NP(68,1)=3
13810        NP(69,1)=3
13820        NP(64,1)=4
13821        NP(64,2)=2
13830        NP(65,1)=3
13831        NP(65,2)=4
13832        NP(65,3)=4
13840        NP(66,1)=3
13842        NP(66,3)=2
13850        NP(61,1)=2
13860        NP(62,1)=1
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13880        NP(58,1)=2
13890        NP(59,1)=4
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13930        NP(57,1)=2
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13950        NP(53,1)=3
13960        NP(54,1)=2
13970        NP(49,1)=1
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13980        NP(50,1)=4
13982        NP(50,3)=2
13990        NP(51,1)=1
14000        NP(46,1)=2
14010        NP(47,1)=4
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14050        NP(45,1)=4
14060        NP(40,1)=2
14070        NP(41,1)=1
14080        NP(42,1)=2
```

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14090       NP(37,1)=2
14100       NP(38,1)=1
14110       NP(39,1)=2
14120       NP(34,1)=1
14121       NP(34,2)=3
14130       NP(35,1)=3
14140       NP(36,1)=2
14150       NP(31,1)=1
14160       NP(32,1)=2
14170       NP(33,1)=2
14180       NP(28,1)=2
14190       NP(29,1)=1
14200       NP(30,1)=2
14210       NP(25,1)=1
14220       NP(26,1)=3
14230       NP(27,1)=2
14240       NP(22,1)=1
14250       NP(23,1)=4
14260       NP(24,1)=4
14270       NP(19,1)=3
14280       NP(20,1)=3
14290       NP(21,1)=2
14300       NP(16,1)=2
14310       NP(17,1)=1
14320       NP(18,1)=3
14330       NP(13,1)=3
14331       NP(13,2)=1
14332       NP(13,3)=1
14340       NP(14,1)=3
14350       NP(15,1)=2
14360       NP(10,1)=3
14370       NP(11,1)=4
14380       NP(12,1)=3
14390       NP(7,1)=2
14391       NP(7,2)=4
14392       NP(7,3)=4
14400       NP(8,1)=4
14410       NP(9,1)=4
14420       NP(4,1)=1
14421       NP(4,2)=3
14430       NP(5,1)=4
14440       NP(6,1)=1
14450       NP(1,1)=3
14460       NP(2,1)=4
14470       NP(3,1)=3
14480       DO 20 I=1,438
14490       IF(NP(I,2) .EQ. 0) NP(I,2)=NP(I,1)
14500       IF(NP(I,3) .EQ. 0) NP(I,3)=NP(I,1)
14510    20 CONTINUE
14520       RETURN
14530       END
23440       SUBROUTINE GC(MGC)
```

```
23450       DIMENSION MGC(16,4)
23460       MGC(1,1)=15
23470       MGC(2,1)=17
23480       MGC(3,1)=4
23490       MGC(4,1)=16
23500       MGC(5,1)=3
23510       MGC(6,1)=20
23520       MGC(7,1)=4
23530       MGC(8,1)=25
23540       MGC(9,1)=15
23550       MGC(10,1)=17
23560       MGC(11,1)=4
23570       MGC(12,1)=16
23580       MGC(13,1)=3
23590       MGC(14,1)=25
23600       MGC(15,1)=4
23610       MGC(16,1)=25
23620       MGC(1,2)=5
23630       MGC(2,2)=1
23640       MGC(3,2)=2
23650       MGC(4,2)=10
23660       MGC(5,2)=5
23670       MGC(6,2)=1
23680       MGC(7,2)=2
23690       MGC(8,2)=8
23700       MGC(9,2)=5
23710       MGC(10,2)=1
23720       MGC(11,2)=2
23730       MGC(12,2)=10
23740       MGC(13,2)=5
23750       MGC(14,2)=1
23760       MGC(15,2)=2
23770       MGC(16,2)=8
23780       MGC(1,3)=3
23790       MGC(2,3)=12
23800       MGC(3,3)=9
23810       MGC(4,3)=18
23820       MGC(5,3)=3
23830       MGC(6,3)=12
23840       MGC(7,3)=9
23850       MGC(8,3)=14
23860       MGC(9,3)=3
23870       MGC(10,3)=12
23880       MGC(11,3)=9
23890       MGC(12,3)=18
23900       MGC(13,3)=3
23910       MGC(14,3)=12
23920       MGC(15,3)=9
23930       MGC(16,3)=14
23940       MGC(1,4)=11
23950       MGC(2,4)=4
23960       MGC(3,4)=7
```

```
23970        MGC(4,4)=13
23980        MGC(5,4)=19
23990        MGC(6,4)=12
24000        MGC(7,4)=2
24010        MGC(8,4)=6
24020        MGC(9,4)=11
24230        MGC(10,4)=4
24040        MGC(11,4)=7
24050        MGC(12,4)=13
24060        MGC(13,4)=11
24070        MGC(14,4)=12
24080        MGC(15,4)=7
24090        MGC(16,4)=6
24100        RETURN
24110        END
40010        SUBROUTINE INIT1(NP,MP,MGC)
40020        DIMENSION NP(450,4),MP(150,4),MGC(16,4)
40025        DO 10 I=1,3
40030        J=146
40040    12  J3=J*3
40050        J31=J3-1
40060        J32=J3-2
40070        NIP=4*NP(J32,2)+NP(J31,2)-4
40080        MP(J,2)=MGC(NIP,NP(J3,2))
40090        J=J-1
40100        IF (J.GE.1)  GO TO 12
40105    10  CONTINUE
40110        RETURN
40120        END
50010        subroutine init3(np,mp,mgc)
50020        DIMENSION NP(450,4),MP(150,4),MGC(16,4)
50030        J=146
50040    12  J3=J*3
50050        J31=J3-1
50060        J32=J3-2
50070        NIP=4*NP(J32,3)+NP(J31,3)-4
50080        MP(J,3)=MGC(NIP,NP(J3,3))
50090        J=J-1
50100        IF (J.GE.1)  GO TO 12
50110        RETURN
50120        END
60010        SUBROUTINE AAAR(MCRIT)
60020        DIMENSION MCRIT(146,14)
60030        MCRIT(1,3)= 7
60040        MCRIT(1,4)=19
60050        MCRIT(1,5)= 9
60060        MCRIT(1,6)= 1
60070        MCRIT(1,7)=25
60080        MCRIT(2,2)=10
60090        MCRIT(2,3)=12
60100        MCRIT(2,4)=18
60110        MCRIT(2,5)= 3
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60120        MCRIT(2,6)=14
60130        MCRIT(2,7)= 8
60140        MCRIT(2,8)=25
60150        MCRIT(2,9)=13
60160        MCRIT(2,10)=16
60170        MCRIT(3,2)= 3
60180        MCRIT(3,3)= 6
60190        MCRIT(3,4)=15
60200        MCRIT(3,5)=20
60210        MCRIT(3,6)=25
60220        MCRIT(4,2)= 7
60230        MCRIT(4,3)= 4
60240        MCRIT(4,4)= 2
60250        MCRIT(4,5)=25
60260        MCRIT(5,2)= 9
60270        MCRIT(5,3)=10
60280        MCRIT(9,5)=13
60290        MCRIT(12,11)= 5
60300        MCRIT(13,2)= 2
60310        MCRIT(12,7)= 3
60320        MCRIT(12,8)=10
60330        MCRIT(12,9)=12
60340        MCRIT(12,10)=11
60350        MCRIT(13,3)= 1
60360        MCRIT(13,4)= 7
60370        MCRIT(13,5)= 4
60380        MCRIT(13,6)=17
60390        MCRIT(13,7)=13
60400        MCRIT(14,2)= 3
60410        MCRIT(9,6)= 7
60420        MCRIT(9,7)= 5
60430        MCRIT(9,8)=10
60440        MCRIT(9,9)=17
60450        MCRIT(9,10)= 1
60460        MCRIT(9,11)=14
60470        MCRIT(10,2)= 2
60480        MCRIT(10,3)= 7
60490        MCRIT(10,4)=18
60500        MCRIT(10,5)= 3
60510        MCRIT(10,6)=14
60520        MCRIT(10,7)= 4
60530        MCRIT(10,8)= 8
60540        MCRIT(11,2)= 5
60550        MCRIT(11,3)= 1
60560        MCRIT(11,4)=11
60570        MCRIT(11,5)= 3
60580        MCRIT(11,6)=14
60590        MCRIT(11,7)= 4
60600        MCRIT(11,8)= 8
60610        MCRIT(12,2)= 6
60620        MCRIT(12,3)= 7
60630        MCRIT(12,4)= 4
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60640        MCRIT(12,5)=13
60650        MCRIT(12,6)= 2
60660        MCRIT(5,4)= 4
60670        MCRIT(5,5)= 1
60680        MCRIT(5,6)= 8
60690        MCRIT(5,7)= 2
60700        MCRIT(5,8)= 6
60710        MCRIT(5,9)=25
60720        MCRIT(6,2)= 4
60730        MCRIT(6,3)= 8
60740        MCRIT(6,4)= 2
60750        MCRIT(6,5)=10
60760        MCRIT(6,6)= 1
60770        MCRIT(6,7)= 6
60780        MCRIT(6,8)=14
60790        MCRIT(6,9)= 9
60800        MCRIT(6,10)= 5
60810        MCRIT(6,11)=25
60820        MCRIT(7,2)= 8
60830        MCRIT(7,3)= 2
60840        MCRIT(7,4)= 1
60850        MCRIT(7,5)=10
60860        MCRIT(7,6)=21
60870        MCRIT(7,7)=13
60880        MCRIT(7,8)=14
60890        MCRIT(7,9)= 6
60900        MCRIT(8,2)= 6
60910        MCRIT(8,3)=10
60920        MCRIT(8,4)= 4
60930        MCRIT(9,2)=18
60940        MCRIT(9,3)= 4
60950        MCRIT(9,4)= 2
60960        MCRIT(14,3)= 4
60970        MCRIT(14,4)=15
60980        MCRIT(14,5)=12
60990        MCRIT(15,2)=20
61000        MCRIT(15,3)=15
61010        MCRIT(15,4)= 1
61020        MCRIT(15,5)= 4
61030        MCRIT(16,2)= 1
61040        MCRIT(16,3)= 4
61050        MCRIT(16,4)= 2
61060        MCRIT(16,5)=10
61070        MCRIT(16,6)=12
61080        MCRIT(17,2)= 6
61090        MCRIT(17,3)=11
61100        MCRIT(17,4)= 8
61110        MCRIT(17,5)=18
61120        MCRIT(18,2)= 5
61130        MCRIT(18,3)= 6
61140        MCRIT(18,4)=11
61150        MCRIT(18,5)=18
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61160          MCRIT(19,2)=13
61170          MCRIT(19,3)= 6
61180          MCRIT(19,4)=18
61190          MCRIT(19,5)=21
61200          MCRIT(19,6)= 1
61210          MCRIT(19,7)=14
61220          MCRIT(19,8)= 8
61230          MCRIT(19,9)= 2
61240          MCRIT(19,10)=10
61250          MCRIT(20,2)= 5
61260          MCRIT(20,3)= 2
61270          MCRIT(20,4)= 4
61280          MCRIT(20,5)= 8
61290          MCRIT(20,6)= 3
61300          MCRIT(20,7)=11
61310          MCRIT(20,8)=10
61320          MCRIT(20,9)= 1
61330          MCRIT(20,10)= 9
61340          MCRIT(21,2)=10
61350          MCRIT(21,3)= 8
61360          MCRIT(21,4)=13
61370          MCRIT(21,5)=18
61380          MCRIT(21,6)= 2
61390          MCRIT(21,7)= 1
61400          MCRIT(21,8)=14
61410          MCRIT(21,9)=13
61420          MCRIT(21,10)= 8
61430          MCRIT(22,2)= 8
61440          MCRIT(22,3)=10
61450          MCRIT(22,4)= 6
61460          MCRIT(22,5)= 2
61470          MCRIT(22,6)=13
61480          MCRIT(22,7)=14
61490          MCRIT(23,2)= 5
61500          MCRIT(23,3)=10
61510          MCRIT(23,4)= 2
61520          MCRIT(23,5)= 7
61530          MCRIT(23,6)=17
61540          MCRIT(23,7)=11
61550          MCRIT(23,8)=25
61560          MCRIT(23,9)= 3
61570          MCRIT(24,2)= 1
61580          MCRIT(24,3)= 3
61590          MCRIT(24,4)=12
61600          MCRIT(24,5)= 5
61610          MCRIT(25,2)= 1
61620          MCRIT(25,3)= 6
61630          MCRIT(25,4)= 2
61640          MCRIT(25,5)=12
61650          MCRIT(26,2)= 8
61660          MCRIT(26,3)=14
61670          MCRIT(26,4)=16
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61680        MCRIT(26,5)= 6
61690        MCRIT(27,2)= 2
61700        MCRIT(27,3)=18
61710        MCRIT(27,4)= 7
61720        MCRIT(28,2)= 3
61730        MCRIT(28,3)= 9
61740        MCRIT(29,2)= 1
61750        MCRIT(29,3)= 2
61760        MCRIT(30,2)=12
61770        MCRIT(30,3)= 4
61780        MCRIT(31,2)= 3
61790        MCRIT(32,2)= 3
61800        MCRIT(33,2)= 5
61810        MCRIT(33,3)= 3
61820        MCRIT(33,4)=11
61830        MCRIT(34,2)= 5
61840        MCRIT(35,2)=16
61850        MCRIT(35,3)=15
61860        MCRIT(36,2)= 9
61870        MCRIT(37,2)=20
61880        MCRIT(37,3)= 4
61890        MCRIT(38,2)= 7
61900        MCRIT(39,2)=14
61910        MCRIT(39,3)=12
61920        MCRIT(39,4)= 8
61930        MCRIT(39,5)= 4
61940        MCRIT(40,2)=12
61950        MCRIT(41,2)=15
61960        MCRIT(41,3)=16
61970        MCRIT(42,2)=15
61980        MCRIT(42,3)= 4
61990        MCRIT(43,2)= 8
62000        MCRIT(43,3)= 4
62010        MCRIT(43,4)=10
62020        MCRIT(43,5)=14
62030        MCRIT(43,6)= 7
62040        MCRIT(43,7)= 2
62050        MCRIT(43,8)=12
62060        MCRIT(44,2)= 4
62070        MCRIT(44,3)=18
62080        MCRIT(44,4)= 7
62090        MCRIT(44,5)=14
62100        MCRIT(44,6)= 2
62110        MCRIT(44,7)= 8
62120        MCRIT(45,2)=15
62130        MCRIT(45,3)= 3
62140        MCRIT(46,2)= 1
62150        MCRIT(46,3)= 8
62160        MCRIT(47,2)=10
62170        MCRIT(47,3)= 2
62180        MCRIT(47,4)=13
62190        MCRIT(48,2)= 3
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62200        MCRIT(49,2)= 4
62210        MCRIT(49,3)= 1
62220        MCRIT(50,2)= 7
62230        MCRIT(50,3)= 4
62240        MCRIT(50,4)=13
62250        MCRIT(50,5)=10
62260        MCRIT(50,6)= 6
62270        MCRIT(51,2)= 9
62280        MCRIT(51,3)= 2
62290        MCRIT(52,2)=10
62300        MCRIT(52,3)=13
62310        MCRIT(52,4)= 4
62320        MCRIT(52,5)=18
62330        MCRIT(52,6)= 1
62340        MCRIT(52,7)= 6
62350        MCRIT(52,8)= 8
62360        MCRIT(52,9)= 2
62370        MCRIT(53,2)= 2
62380        MCRIT(54,2)= 5
62390        MCRIT(54,3)=11
62400        MCRIT(55,2)=19
62410        MCRIT(55,3)= 3
62420        MCRIT(55,4)=17
62430        MCRIT(56,2)= 1
62440        MCRIT(56,3)=13
62450        MCRIT(56,4)= 4
62460        MCRIT(56,5)=10
62470        MCRIT(56,6)= 2
62480        MCRIT(56,7)=18
62490        MCRIT(56,8)=25
62500        MCRIT(57,2)=13
62510        MCRIT(57,3)=10
62520        MCRIT(57,4)= 2
62530        MCRIT(58,2)= 9
62540        MCRIT(58,3)= 2
62550        MCRIT(58,4)=12
62560        MCRIT(58,5)=25
62570        MCRIT(59,2)= 6
62580        MCRIT(59,3)= 8
62590        MCRIT(59,4)= 7
62600        MCRIT(59,5)=25
62610        MCRIT(59,6)=19
62620        MCRIT(59,7)=14
62630        MCRIT(60,2)= 5
62640        MCRIT(61,2)= 6
62650        MCRIT(61,3)= 3
62660        MCRIT(61,4)=13
62670        MCRIT(61,5)= 8
62680        MCRIT(61,6)=12
62690        MCRIT(62,2)= 2
62700        MCRIT(62,3)= 1
62710        MCRIT(63,2)=18
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62720         MCRIT(63,3)=12
62730         MCRIT(63,4)=16
62740         MCRIT(64,2)= 1
62750         MCRIT(65,2)= 6
62760         MCRIT(65,3)= 4
62770         MCRIT(65,4)= 2
62780         MCRIT(65,5)= 8
62790         MCRIT(66,2)= 6
62800         MCRIT(66,3)= 8
62810         MCRIT(67,2)= 5
62820         MCRIT(67,3)= 2
62830         MCRIT(67,4)=10
62840         MCRIT(67,5)= 8
62850         MCRIT(68,2)= 3
62860         MCRIT(68,3)=11
62870         MCRIT(69,2)= 8
62880         MCRIT(69,3)=12
62890         MCRIT(69,4)= 9
62900         MCRIT(69,5)= 1
62910         MCRIT(69,6)= 7
62920         MCRIT(69,7)= 2
62930         MCRIT(69,8)= 4
62940         MCRIT(69,9)=10
62950         MCRIT(69,10)=13
62960         MCRIT(69,11)=18
62970         MCRIT(69,12)= 5
62980         MCRIT(69,13)=14
62990         MCRIT(70,2)= 2
63000         MCRIT(70,3)= 7
63010         MCRIT(70,4)= 4
63020         MCRIT(71,2)=15
63030         MCRIT(71,3)= 3
63040         MCRIT(71,4)=11
63050         MCRIT(71,5)= 4
63060         MCRIT(72,2)= 4
63070         MCRIT(72,3)=17
63080         MCRIT(72,4)= 1
63090         MCRIT(72,5)= 2
63100         MCRIT(72,6)=10
63110         MCRIT(72,7)=13
63120         MCRIT(73,2)=10
63130         MCRIT(73,3)= 8
63140         MCRIT(73,4)=14
63150         MCRIT(73,5)=13
63160         MCRIT(73,6)= 4
63170         MCRIT(74,2)= 1
63180         MCRIT(74,3)= 2
63190         MCRIT(74,4)=10
63200         MCRIT(75,2)= 3
63210         MCRIT(75,3)= 5
63220         MCRIT(75,4)=19
63230         MCRIT(75,5)=11
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63240        MCRIT(75,6)= 7
63250        MCRIT(76,2)= 2
63260        MCRIT(76,3)=13
63270        MCRIT(76,4)= 4
63280        MCRIT(76,5)= 7
63290        MCRIT(76,6)=18
63300        MCRIT(76,7)= 6
63310        MCRIT(76,8)= 1
63320        MCRIT(76,9)=14
63330        MCRIT(76,10)= 8
63340        MCRIT(77,2)=18
63350        MCRIT(77,3)=13
63360        MCRIT(77,4)= 8
63370        MCRIT(77,5)=14
63380        MCRIT(77,6)=10
63390        MCRIT(77,7)=14
63400        MCRIT(78,2)= 3
63410        MCRIT(78,3)= 9
63420        MCRIT(79,2)=10
63430        MCRIT(79,3)= 8
63440        MCRIT(79,4)=13
63450        MCRIT(80,2)=13
63460        MCRIT(80,3)=10
63470        MCRIT(80,4)= 6
63480        MCRIT(80,5)= 4
63490        MCRIT(81,2)= 3
63500        MCRIT(81,3)=11
63510        MCRIT(82,2)= 6
63520        MCRIT(83,2)= 2
63530        MCRIT(83,3)= 1
63540        MCRIT(83,4)=13
63550        MCRIT(84,2)= 7
63560        MCRIT(84,3)= 2
63570        MCRIT(84,4)=18
63580        MCRIT(85,2)=15
63590        MCRIT(85,3)=16
63600        MCRIT(86,2)= 2
63610        MCRIT(86,3)= 4
63620        MCRIT(87,2)= 7
63630        MCRIT(87,3)= 4
63640        MCRIT(87,4)= 6
63650        MCRIT(87,5)=14
63660        MCRIT(87,6)= 2
63670        MCRIT(87,7)= 8
63680        MCRIT(87,8)=18
63690        MCRIT(87,9)=13
63700        MCRIT(88,2)= 3
63710        MCRIT(88,3)=12
63720        MCRIT(88,4)= 9
63730        MCRIT(89,2)= 4
63740        MCRIT(89,3)= 7
63750        MCRIT(90,2)= 8
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63760         MCRIT(90,3)=14
63770         MCRIT(90,4)= 6
63780         MCRIT(91,2)= 3
63790         MCRIT(91,3)=16
63800         MCRIT(91,4)= 9
63810         MCRIT(91,5)=25
63820         MCRIT(92,2)=18
63830         MCRIT(92,3)=16
63840         MCRIT(92,4)=25
63850         MCRIT(93,2)=17
63860         MCRIT(93,3)= 4
63870         MCRIT(93,4)=25
63880         MCRIT(94,2)=10
63890         MCRIT(94,3)= 5
63900         MCRIT(94,4)=13
63910         MCRIT(95,2)= 6
63920         MCRIT(95,3)= 2
63930         MCRIT(95,4)=25
63940         MCRIT(95,5)= 8
63950         MCRIT(95,6)=14
63960         MCRIT(96,2)= 3
63970         MCRIT(97,2)=18
63980         MCRIT(97,3)=14
63990         MCRIT(97,4)=12
64000         MCRIT(98,2)= 5
64010         MCRIT(98,3)=19
64020         MCRIT(99,2)=10
64030         MCRIT(99,3)=13
64040         MCRIT(99,4)=18
64050         MCRIT(99,5)=16
64060         MCRIT(100,2)= 9
64070         MCRIT(101,2)= 8
64080         MCRIT(101,3)=14
64090         MCRIT(101,4)= 2
64100         MCRIT(102,2)=13
64110         MCRIT(102,3)=10
64120         MCRIT(102,4)= 6
64130         MCRIT(102,5)= 7
64140         MCRIT(103,2)=15
64150         MCRIT(104,2)=12
64160         MCRIT(104,3)= 6
64170         MCRIT(104,4)=13
64180         MCRIT(105,2)= 3
64190         MCRIT(105,3)=12
64200         MCRIT(106,2)= 3
64210         MCRIT(107,2)= 1
64220         MCRIT(108,2)=13
64230         MCRIT(108,3)=10
64240         MCRIT(109,2)= 5
64250         MCRIT(109,3)=19
64260         MCRIT(109,4)= 4
64270         MCRIT(109,5)=11
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64280        MCRIT(109,6)= 2
64290        MCRIT(110,2)= 3
64300        MCRIT(110,3)=11
64310        MCRIT(110,4)=15
64320        MCRIT(110,5)= 5
64330        MCRIT(111,2)= 5
64340        MCRIT(111,3)=21
64350        MCRIT(111,4)= 2
64360        MCRIT(111,5)=11
64370        MCRIT(112,2)=17
64380        MCRIT(112,3)=11
64390        MCRIT(112,4)= 4
64400        MCRIT(112,5)= 5
64410        MCRIT(112,6)=18
64420        MCRIT(112,7)=11
64430        MCRIT(113,2)= 5
64440        MCRIT(113,3)=17
64450        MCRIT(113,4)= 8
64460        MCRIT(113,5)= 2
64470        MCRIT(114,2)= 3
64480        MCRIT(115,2)= 2
64490        MCRIT(115,3)= 1
64500        MCRIT(115,4)= 4
64510        MCRIT(116,2)=18
64520        MCRIT(116,3)=10
64530        MCRIT(116,4)=12
64540        MCRIT(116,5)= 7
64550        MCRIT(116,6)= 8
64560        MCRIT(116,7)=13
64570        MCRIT(117,2)=18
64580        MCRIT(117,3)=13
64590        MCRIT(117,4)=12
64600        MCRIT(118,2)=15
64610        MCRIT(118,3)= 3
64620        MCRIT(118,4)=18
64630        MCRIT(119,2)= 1
64640        MCRIT(119,3)=14
64650        MCRIT(119,4)=15
64660        MCRIT(119,5)= 4
64670        MCRIT(119,6)= 6
64680        MCRIT(119,7)=10
64690        MCRIT(120,2)= 6
64700        MCRIT(120,3)=10
64710        MCRIT(120,4)=13
64720        MCRIT(120,5)= 4
64730        MCRIT(120,6)=18
64740        MCRIT(120,7)= 8
64750        MCRIT(121,2)= 8
64760        MCRIT(121,3)=10
64770        MCRIT(121,4)=14
64780        MCRIT(121,5)=13
64790        MCRIT(121,6)= 6
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64800         MCRIT(122,2)=15
64810         MCRIT(123,2)= 7
64820         MCRIT(123,3)=10
64830         MCRIT(123,4)= 4
64840         MCRIT(123,5)=13
64850         MCRIT(124,2)= 9
64860         MCRIT(124,3)=11
64870         MCRIT(124,4)=12
64880         MCRIT(125,2)= 9
64890         MCRIT(125,3)= 2
64900         MCRIT(125,4)=14
64910         MCRIT(125,5)=12
64920         MCRIT(125,6)= 8
64930         MCRIT(125,7)= 5
64940         MCRIT(125,8)= 3
64950         MCRIT(125,9)= 1
64960         MCRIT(125,10)=10
64970         MCRIT(125,11)=17
64980         MCRIT(126,2)= 5
64990         MCRIT(126,3)= 2
65000         MCRIT(126,4)= 3
65010         MCRIT(126,5)=19
65020         MCRIT(126,6)= 7
65030         MCRIT(126,7)= 8
65040         MCRIT(126,8)=17
65050         MCRIT(127,2)=14
65060         MCRIT(127,3)= 8
65070         MCRIT(127,4)= 3
65080         MCRIT(128,2)= 2
65090         MCRIT(128,3)= 5
65100         MCRIT(128,4)=18
65110         MCRIT(128,5)= 4
65120         MCRIT(129,2)= 2
65130         MCRIT(129,3)= 4
65140         MCRIT(129,4)=10
65150         MCRIT(129,5)=14
65160         MCRIT(129,6)= 8
65170         MCRIT(129,7)= 1
65180         MCRIT(129,8)=13
65190         MCRIT(130,2)=16
65200         MCRIT(130,3)=20
65210         MCRIT(130,4)=18
65220         MCRIT(130,5)= 3
65230         MCRIT(130,6)=15
65240         MCRIT(130,7)=10
65250         MCRIT(131,2)=14
65260         MCRIT(131,3)= 8
65270         MCRIT(131,4)= 3
65280         MCRIT(132,2)= 6
65290         MCRIT(132,3)= 2
65300         MCRIT(132,4)=14
65310         MCRIT(132,5)= 8
```

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65320        MCRIT(133,2)= 5
65330        MCRIT(133,3)=19
65340        MCRIT(133,4)= 3
65350        MCRIT(133,5)=18
65360        MCRIT(134,2)= 5
65370        MCRIT(134,3)=15
65380        MCRIT(135,2)= 2
65390        MCRIT(135,3)= 7
65400        MCRIT(135,4)=17
65410        MCRIT(135,5)= 4
65420        MCRIT(135,6)=12
65430        MCRIT(136,2)= 1
65440        MCRIT(136,3)= 2
65450        MCRIT(136,4)=10
65460        MCRIT(136,5)= 5
65470        MCRIT(137,2)= 5
65480        MCRIT(138,2)= 1
65490        MCRIT(138,3)= 2
65500        MCRIT(138,4)= 4
65510        MCRIT(139,2)=13
65520        MCRIT(139,3)= 2
65530        MCRIT(139,4)=10
65540        MCRIT(139,5)= 7
65550        MCRIT(139,6)= 4
65560        MCRIT(139,7)=18
65570        MCRIT(140,2)= 2
65580        MCRIT(141,2)= 3
65590        MCRIT(141,3)=12
65600        MCRIT(142,2)= 2
65610        MCRIT(142,3)= 4
65620        MCRIT(142,4)= 1
65630        MCRIT(143,2)=18
65640        MCRIT(143,3)= 4
65650        MCRIT(143,4)= 6
65660        MCRIT(143,5)=12
65670        MCRIT(144,2)= 6
65680        MCRIT(144,3)=12
65690        MCRIT(144,4)= 2
65700        MCRIT(145,2)=16
65710        MCRIT(145,3)=17
65720        MCRIT(145,4)=18
65730        MCRIT(146,2)=18
65740        MCRIT(146,3)=10
65750        RETURN
65760        END
70080        SUBROUTINE INIT(IX,IXS,F,E,N,INTER,NCOUNT,
70090       1MCOUNT,NULL,NA,MA,M,MGC,NP,NIP,NR,MR,MP,IH,
70091       1MCH,MCR,MCA)
70100        INTEGER E,F
70110        DIMENSION NA(438,50),MA(146,50),NULL(438),
70111       1PCT(438),NCOUNT(4,4)
70120        DIMENSION MCOUNT(28,28),MGC(16,4),N(450),M(150),
```

```
70121       1NP(450,4)
70130        DIMENSION NR(438),MR(146),MP(150,4),MCH(150),
70131       1MCR(150),MCA(150)
70140        IX=IXS
70150        E=1
70160        F=1
70170        MCH(147)=0
70180        MCR(147)=0
70190        MCA(147)=0
70200        N(439)=2
70210        DO 13 I=1,4
70220        DO 13 J=1,4
70230        NCOUNT(I,J)=0
70240     13 CONTINUE
70250        DO 14 J=1,28
70260        DO 14 I=1,28
70270        MCOUNT(I,J)=0
70280     14 CONTINUE
70290        DO 15 I=1,438
70300        NULL(I)=0
70310        NA(I,1)=1
70320        NR(I)=0
70330        PCT(I)=0.000
70340        DO 151 J=2,50
70350        NA(I,J)=0
70360    151 CONTINUE
70370     15 CONTINUE
70380        DO 141 I=1,146
70390        MA(I,1)=1
70400        MR(I)=0
70410        M(I)=MP(I,IH)
70420        MCH(I)=0
70430        MCR(I)=0
70440        MCA(I)=0
70450        DO 1411 J=2,50
70460        MA(I,J)=0
70470   1411 CONTINUE
70480    141 CONTINUE
70490        DO 101 I=1,438
70500        N(I)=NP(I,IH)
70510    101 CONTINUE
70520        DO 1011 I=1,146,7
70530   1011 CONTINUE
70540        RETURN
70550        END
80010        SUBROUTINE TRANF(A,B1,B2,B3,C1,C2,C3,D1,D2,D3,E1,
80011       1E1,E2,E3,K)
80020        INTEGER K
80030        A=0.3971
80040        IF (K.EQ.2)  GO TO 20
80050        IF (K.EQ.3)  GO TO 30
80060 C   *******FROM ZUCKERKANDL(1971)***********
```

```
80070         C1=0.061
80080         C2=0.097
80090         C3=0.166
80100         D1=0.085
80110         D2=0.183
80120         D3=0.342
80130         E1=0.038
80140         E2=0.130
80150         E3=0.219
80160         B1=0.058
80170         B2=0.179
80180         B3=0.273
80190         GO TO 40
80200      20 CONTINUE
80210 C    *******FROM FITCH(1967)***********
80220         C1=0.0113
80230         C2=0.0113
80240         C3=0.0715
80250         D1=0.0458
80260         D2=0.1447
80270         D3=0.2407
80280         E1=0.0277
80290         E2=0.0912
80300         E3=0.2907
80310         B1=0.1140
80320         B2=0.2377
80330         B3=0.3971
80340         GO TO 40
80350      30 CONTINUE
80360 C    ******************FROM DAYHOFF-P.226***********
80370         C1=0.0244
80380         C2=0.0975
80390         C3=0.1463
80400         D1=0.0122
80410         D2=0.0976
80420         D3=0.3903
80430         E1=0.0610
80440         E2=0.1586
80450         E3=0.2318
80460         B1=0.0366
80470         B2=0.1464
80480         B3=0.2318
80490      40 RETURN
80500         END
90010         SUBROUTINE TRAN1(NUC,I,INTER,N,IX)
90020         DIMENSION N(450)
90030         NUC=N(I)
90040         B=0.066666667
90050         C=0.033333333
90060         CALL RANDOM (IX,P)
90070         IF (P.GT.0.1)  GO TO 33
90080         IF (P.LE.0.0)  GO TO 33
```

```
90090        IF (P.GE.B)  GO TO 31
90100        IF (P.LE.C)  GO TO 32
90110        N(I)=N(I)+1
90120        GO TO 33
90130     31 N(I)=N(I)+2
90140        GO TO 33
90150     32 N(I)=N(I)+3
90160     33 CONTINUE
90170        IF (N(I).GE.5) N(I)=N(I)-4
90180        RETURN
90190        END
100010        SUBROUTINE MUTATE(I,MCRIT,NULL,NUC,NCOUNT,
100020       1MCOUNT,NA,MA,N,M,MGC,E,F,NR,MR)
100030        INTEGER E,F
100040        DIMENSION NA(438,50),MA(146,50),NULL(438),
100041       1NCOUNT(4,4)
100050        DIMENSION MCOUNT(28,28),MCRIT(146,14),N(450)
100060        DIMENSION MGC(16,4),NR(438),MR(146),M(150)
100070        JIN=1+((I-1)/3)
100080        J3=3*JIN
100090        J31=J3-1
100100        J32=J3-2
100110        NIP=4*N(J32)+N(J31)-4
100120        IF (M(JIN).EQ.MGC(NIP,N(J3)))  GO TO 30
100130     50 ICRIT=JIN
100140        K=1
100150        DO 51 IC=2,14
100160        IF (MGC(NIP,N(J3)).EQ.MCRIT(ICRIT,IC))  K=2
100170     51 CONTINUE
100180        IF (K.EQ.2)  GO TO 34
100190        NULL(I)=NULL(I)+1
100200        N(I)=NUC
100210        GO TO 30
100220     34 CONTINUE
100230        NCOUNT(NUC,N(I))=NCOUNT(NUC,N(I))+1
100240        MCOUNT(M(JIN),MGC(NIP,N(J3)))=MCOUNT(M(JIN),
100241       1MGC(NIP,N(J3)))+1
100250        E=NA(I,1)+1
100260        IF (E.GE.50)  E=50
100270        NA(I,E)=NUC
100280        IP1=0
100290        DO 130 IP=2,50
100300        IPIT=NA(I,IP)
100310        IF (IPIT.EQ.N(I)) IP1=1
100320    130 CONTINUE
100330        NA(I,1)=NA(I,1)+1
100340        F=MA(JIN,1)+1
100350        IF (F.GE.50)  F=50
100360      1 MA(JIN,F)=M(JIN)
100370        IP2=0
100380        DO 131 IP=2,50
100390        IPIT=MA(JIN,IP)
```

```
100400        IF (IPIT.EQ.M(JIN)) IP2=1
100410    131 CONTINUE
100420        MA(JIN,1)=MA(JIN,1)+1
100430        M(JIN)=MGC(NIP,N(J3))
100440     30 CONTINUE
100450        IF (IP1.EQ.1) NR(I)=NR(I)+1
100460        IF (IP2.EQ.1) MR(JIN)=MR(JIN)+1
100470        IP1=0
100480        IP2=0
100490        RETURN
100500        END
110010        SUBROUTINE OUT(M,N,NA,MA,NULL,MCOUNT,NCOUNT,
110020       1HB,IXS,METH,INTER,NR,MR,MCH,MCR,MCA,MP)
110030        DIMENSION NA(438,50),MA(146,50),NULL(438),
110031       1PCT(438)
110040        DIMENSION NCOUNT(4,4),MCOUNT(28,28),N(450),
110041       1M(150)
110050        DIMENSION NR(438),MR(146),MCH(150),MCR(150),
110051       1MCA(150)
110060        DIMENSION MP(150,4)
110070        DO 1000 I=1,21
110080        MCOUNT(I,21)=MCOUNT(I,25)
110090        MCOUNT(21,I)=MCOUNT(25,I)
110100        MCOUNT(21,21)=MCOUNT(25,25)
110110        DO 1001 J=1,21
110120        IVAL=MCOUNT(I,J)
110130        WRITE (10,100) (HB,METH,IXS,INTER,IVAL)
110140    1001 CONTINUE
110150    1000 CONTINUE
110160        DO 1002 I=1,4
110170        DO 1003 J=1,4
110180        IVAL=NCOUNT(I,J)
110190        WRITE (11,100) (HB,METH,IXS,INTER,IVAL)
110200    1003 CONTINUE
110210    1002 CONTINUE
110220        DO 1005 I=1,438
110230        NA(I,1)=NA(I,1)-1
110240        IVAL=NA(I,1)
110250        WRITE (13,100) (HB,METH,IXS,INTER,IVAL)
110260    1005 CONTINUE
110270        DO 1006 I=1,438
110280        IVAL=NR(I)
110290        WRITE (14,100) (HB,METH,IXS,INTER,IVAL)
110300    1006 CONTINUE
110310        DO 1007 I=1,146
110320        IVAL=MR(I)
110330        WRITE (15,100) (HB,METH,IXS,INTER,IVAL)
110340    1007 CONTINUE
110350        DO 1004 I=1,438
110360        IDEM1=I
110370        IVAL=NULL(I)
110380        WRITE (12,100) (HB,METH,IXS,INTER,IVAL)
```

```
110390  1004 CONTINUE
110400       DO 1 J=1,3
110410       DO 2 I=1,146
110420       IF (MP(I,J).EQ.M(I)) GO TO 3
110430       GO TO 2
110440     3 IF (J.EQ.1) MCH(I)=1
110450       IF (J.EQ.2) MCR(I)=1
110460       IF (J.EQ.3) MCA(I)=1
110470     2 CONTINUE
110480     1 CONTINUE
110490       MCH(147)=0
110500       MCR(147)=0
110510       DO 4 I=1,146
110520       MCH(147)=MCH(147)+MCH(I)
110530       MCR(147)=MCR(147)+MCR(I)
110540       MCA(147)=MCA(147)+MCA(I)
110550     4 CONTINUE
110560       DO 5 I=1,147
110570       WRITE (20,100) (HB,METH,IXS,INTER,MCH(I))
110580       WRITE (21,100) (HB,METH,IXS,INTER,MCR(I))
110590       WRITE (22,100) (HB,METH,IXS,INTER,MCA(I))
110600     5 CONTINUE
110610   100 FORMAT (10X,I2,1X,I2,1X,I8,1X,I6,1X,I8)
110620       RETURN
110630       END
120010       SUBROUTINE RANDOM(IX,P)
120020       IY=IX*1220703125
120030       IF(IY)3,4,4
120040     3 IY=IY+2147483647+1
120050     4 RN=IY
120060       RN=RN*0.4656613E-9
120070       P=24.3*RN-10.
120080       IX=IY
120090       RETURN
120100       END
130010       SUBROUTINE RESULT(M,N,NA,MA,NULL,MCOUNT,NCOUNT)
130020       DIMENSION NA(438,50),MA(146,50),NULL(438),
130021      1PCT(438)
130030       DIMENSION NCOUNT(4,4),MCOUNT(28,28),N(450),
130031      1M(150)
130040       IXS=3513
130050       PRINT 38,(M(J),J=1,146)
130060       PRINT 45,((MCOUNT(I,J),I=1,25),J=1,25)
130070       PRINT 391
130080       PRINT 39,(N(I),I=1,438)
130090       PRINT 44,((NCOUNT(I,J),I=1,4),J=1,4)
130100       PRINT 421
130110       DO 40 I=1,438
130120       NA1=NA(I,1)
130130       IF (NA1.EQ.1)  GO TO 40
130140       IF (NA1.GE.50)  NA1=50
130150       PRINT 42,I,(NA(I,J),J=1,NA1)
```

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130160     40 CONTINUE
130170        PRINT 431
130180        DO 41 I=1,146
130190        MA1=MA(I,1)
130200        IF (MA1.EQ.1)  GO TO 41
130210        IF (MA1.GE.25)  MA1=25
130220        PRINT 43,I,(MA(I,J),J=1,MA1)
130230     41 CONTINUE
130240        PRINT 551
130250        DO 56 I=1,438,6
130260        IF (NULL(I).EQ.0)  GO TO 56
130270        PRINT 55,I,NULL(I),NULL(I+1),NULL(I+2),
130280       1NULL(I+3),NULL(I+4),NULL(I+5)
130290     56 CONTINUE
130300        PRINT 531
130310        DO 54 I=1,438
130320        PCT(I)=100.*NA(I,1)/(NA(I,1)+NULL(I))
130330     54 CONTINUE
130340        DO 52 I=1,438,6
130350        PRINT 53,I,PCT(I),PCT(I+1),PCT(I+2),PCT(I+3),
130351       1PCT(I+4),PCT(I+5)
130360     52 CONTINUE
130370     36 FORMAT (15H0ON INTERATION ,I7,10H POSITION ,I4,
130380       16H FROM ,I2,4H TO ,I2)
130390     37 FORMAT (4H AA ,I3,14H CHANGED FROM ,I2,4H TO ,
130391       1I2)
130400     38 FORMAT (20I3)
130410     39 FORMAT (30I2)
130420     42 FORMAT (I4,2X,I2,49I3)
130430     43 FORMAT (I4,2X,I2,24I5)
130440     44 FORMAT (26H0NUCLEID ACID CHANGE TABLE/15X,2HTO/
130441       16H FROM ,3X,1HA,
130450       13X,1HC,3X,1HG,3X,1HT/3X,1HA,2X,4I4/3X,1HC,2X,
130451       14I4/3X,1HG,2X,4I4/
130460       13X,1HT,2X,4I4)
130470     45 FORMAT (25H0 AMINO ACID CHANGE TABLE/39X,2HTO/
130471       16H FROM ,
130480       11HG,2X,1HA,2X,1HL,2X,1HS,2X,1HV,2X,1HK,2X,1HT,
130481       12X,1HE,2X,1HP,
130490       12X,1HD,2X,1HI,2X,1HR,2X,1HN,2X,1HQ,2X,1HF,2X,
130491       1HY,2X,1HC,2X,
130500       11HH,2X,1HM,2X,1HW,12X,4HSTOP/2H G,2X,25I3/2H A,
130501       12X,25I3/2H L,
130510       12X,25I3/2H S,2X,25I3/2H V 2X,25I3/2H K,2X,25I3/
130511       12H T,2X,25I3/
130520       12H E,2X,25I3/2H P,2X,25I3/2H D,2X,25I3/2H I,2X,
130521       125I3/2H R,2X,
130530       125I3/2H N,2X,25I3/2H Q,2X,25I3/2H F,2X,25I3/
130531       12H Y,2X,25I3/2H C,
130540       12X,25I3/2H H,2X,25I3/2H M,2X,25I3/2H W,2X,25I3/
130550       14X,25I3/4X,25I3/4X,25I3/4X,25I3/1X,4HSTOP,25I3)
130560     53 FORMAT(I4,6F10.3)
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130570     55 FORMAT (I4,6I5)
130580    381 FORMAT(21H0STARTING AMINO ACIDS/)
130590    382 FORMAT(19H0ENDING AMINO ACIDS/)
130600    391 FORMAT(21H0ENDING NUCLEIC ACIDS/)
130610    421 FORMAT (34H0 NUCLEOTIDE MUTATIONS BY POSITION//
130611       15H  NA ,5HQUANT/)
130620    431 FORMAT (34H0 AMINO ACID MUTATIONS BY POSITION//
130621       15H  AA ,5HQUANT/)
130630    531 FORMAT (29H0PERCENT ACCEPTABLE MUTATIONS/)
130640    551 FORMAT (46H0 COUNT OF DISALLOWED MUTATIONS BY N
130641       1A POSITION)
130650        RETURN
130660        END
140010        SUBROUTINE TRAN2(NUC,I,INTER,N,K,IX)
140020        INTEGER K
140030        DIMENSION N(450)
140040        NUC=N(I)
140050        CALL RANDOM (IX,P)
140060        IF (P.LT.0.0)  GO TO 341
140070        CALL TRANF(A,B1,B2,B3,C1,C2,C3,D1,D2,D3,E1,E2,
140071       1E3,K)
140080        IF (P.GT.A)  GO TO 341
140090        NUC=N(I)
140100        IF (NUC.EQ.1)  GO TO 31
140110        IF (NUC.EQ.2)  GO TO 32
140120        IF (NUC.EQ.3)  GO TO 33
140130        IF (P.GE.B3)  GO TO 341
140140        IF (P.LE.B1)  N(I)=N(I)-1
140150        IF (P.GE.B2)  N(I)=N(I)+1
140160        N(I)=N(I)-2
140170        GO TO 341
140180     31 IF (P.GE.C3)  GO TO 341
140190        N(I)=N(I)+2
140200        IF (P.LE.C1) N(I)=N(I)-1
140210        IF (P.GE.C2) N(I)=N(I)+1
140220        GO TO 341
140230     32 IF (P.GE.D3)  GO TO 341
140240        N(I)=N(I)+1
140250        IF (P.LE.D1) N(I)=N(I)-2
140260        IF (P.GE.D2) N(I)=N(I)+1
140270        GO TO 341
140280     33 IF (P.GE.E3)  GO TO 341
140290        N(I)=N(I)-1
140300        IF (P.LE.E1) N(I)=N(I)-1
140310        IF (P.GE.E2) N(I)=N(I)+2
140320    341 CONTINUE
140330        RETURN
140340        END
150010        SUBROUTINE TP(T)
150020        DIMENSION T(64,3)
150030        T(1,1)=.0540
150040        T(1,2)=.0016
```

```
150050          T(1,3)=.0191
150060          T(2,1)=.0990
150070          T(2,2)=.0198
150080          T(2,3)=.0911
150090          T(3,1)=.0530
150100          T(3,2)=.0217
150110          T(3,3)=.0337
150120          T(4,1)=.1280
150130          T(4,2)=.0230
150140          T(4,3)=.0952
150150          T(5,1)=.0270
150160          T(5,2)=.0018
150170          T(5,3)=.0198
150180          T(6,1)=.0650
150190          T(6,2)=.0061
150200          T(6,3)=.0488
150210          T(7,1)=.0870
150220          T(7,2)=.0094
150230          T(7,3)=.0220
150240          T(8,1)=.1600
150250          T(8,2)=.0125
150260          T(8,3)=.0972
150270          T(9,1)=.1600
150280          T(9,2)=.0151
150290          T(9,3)=.1540
150300          T(10,1)=.1330
150310          T(10,2)=.0692
150320          T(10,3)=.0745
150330          T(11,1)=.0740
150340          T(11,2)=.0185
150350          T(11,3)=.0423
150360          T(12,1)=.1290
150370          T(12,2)=.0176
150380          T(12,3)=.0997
150390          T(13,1)=.0550
150400          T(13,2)=.0311
150410          T(13,3)=.0517
150420          T(14,1)=.1410
150430          T(14,2)=.0101
150440          T(14,3)=.0831
150450          T(15,1)=.0890
150460          T(15,2)=.0152
150470          T(15,3)=.0684
150480          T(16,1)=.1780
150490          T(16,2)=.0137
150500          T(16,3)=.1301
150510          T(17,1)=.0530
150520          T(17,2)=.0035
150530          T(17,3)=.0282
150540          T(18,1)=.0990
150550          T(18,2)=.0194
150560          T(18,3)=.0893
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150570          T(19,1)=.0530
150580          T(19,2)=.0198
150590          T(19,3)=.0308
150600          T(20,1)=.1260
150610          T(20,2)=.0342
150620          T(20,3)=.0657
150630          T(21,1)=.0240
150640          T(21,2)=.0072
150650          T(21,3)=.0240
150660          T(22,1)=.0650
150670          T(22,2)=.0063
150680          T(22,3)=.0503
150690          T(23,1)=.0870
150700          T(23,2)=.0930
150710          T(23,3)=.0217
150720          T(24,1)=.0870
150730          T(24,2)=.0032
150740          T(24,3)=.0292
150750          T(25,1)=.1600
150760          T(25,2)=.0295
150770          T(25,3)=.1558
150780          T(26,1)=.1330
150790          T(26,2)=.0640
150800          T(26,3)=.0689
150810          T(27,1)=.0740
150820          T(27,2)=.0167
150830          T(27,3)=.0382
150840          T(28,1)=.1290
150850          T(28,2)=.0165
150860          T(28,3)=.0825
150870          T(29,1)=.1600
150880          T(29,2)=.1333
150890          T(29,3)=.1333
150900          T(30,1)=.1350
150910          T(30,2)=.0053
150920          T(30,3)=.0957
150930          T(31,1)=.1240
150940          T(31,2)=.0157
150950          T(31,3)=.1033
150960          T(32,1)=.0740
150970          T(32,2)=.0072
150980          T(32,3)=.0489
150990          T(33,1)=.0540
151000          T(33,2)=.0135
151010          T(33,3)=.0270
151020          T(34,1)=.0990
151030          T(34,2)=.0198
151040          T(34,3)=.0912
151050          T(35,1)=.0530
151060          T(35,2)=.0217
151070          T(35,3)=.0337
151080          T(36,1)=.1280
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151090          T(36,2)=.0199
151100          T(36,3)=.0995
151110          T(37,1)=.0270
151120          T(37,2)=.0000
151130          T(37,3)=.0221
151140          T(38,1)=.0650
151150          T(38,2)=.0061
151160          T(38,3)=.0488
151170          T(39,1)=.0870
151180          T(39,2)=.0094
151190          T(39,3)=.0220
151200          T(40,1)=.1600
151210          T(40,2)=.0125
151220          T(40,3)=.0972
151230          T(41,1)=.1600
151240          T(41,2)=.0205
151250          T(41,3)=.1486
151260          T(42,1)=.1330
151270          T(42,2)=.0692
151280          T(42,3)=.0745
151290          T(43,1)=.0740
151300          T(43,2)=.0185
151310          T(43,3)=.0423
151320          T(44,1)=.1290
151330          T(44,2)=.0183
151340          T(44,3)=.1062
151350          T(45,1)=.0550
151360          T(45,2)=.0467
151370          T(45,3)=.0517
151380          T(46,1)=.1410
151390          T(46,2)=.0101
151400          T(46,3)=.0831
151410          T(47,1)=.0880
151420          T(47,2)=.0152
151430          T(47,3)=.0684
151440          T(48,1)=.1780
151450          T(48,2)=.0123
151460          T(48,3)=.1666
151470          T(49,1)=.0530
151480          T(49,2)=.0035
151490          T(49,3)=.0283
151500          T(50,1)=.0990
151510          T(50,2)=.0194
151520          T(50,3)=.0893
151530          T(51,1)=.0530
151540          T(51,2)=.0198
151550          T(51,3)=.0308
151560          T(52,1)=.1280
151570          T(52,2)=.0259
151580          T(52,3)=.0743
151590          T(53,1)=.0240
151600          T(53,2)=.0032
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151610          T(53,3)=.0240
151620          T(54,1)=.0650
151630          T(54,2)=.0063
151640          T(54,3)=.0503
151650          T(55,1)=.0870
151660          T(55,2)=.0093
151670          T(55,3)=.0217
151680          T(56,1)=.0870
151690          T(56,2)=.0034
151700          T(56,3)=.0428
151710          T(57,1)=.1600
151720          T(57,2)=.0215
151730          T(57,3)=.1569
151740          T(58,1)=.1330
151750          T(58,2)=.0640
151760          T(58,3)=.0689
151770          T(59,1)=.0740
151780          T(59,2)=.0167
151790          T(59,3)=.0382
151800          T(60,1)=.1290
151810          T(60,2)=.0227
151820          T(60,3)=.0992
151830          T(61,1)=.1600
151840          T(61,2)=.1333
151850          T(61,3)=.1333
151860          T(62,1)=.1350
151870          T(62,2)=.0101
151880          T(62,3)=.0605
151890          T(63,1)=.1240
151900          T(63,2)=.0231
151910          T(63,3)=.0938
151920          T(64,1)=.0740
151930          T(64,2)=.0072
151940          T(64,3)=.0489
151950          RETURN
151960          END
160080          SUBROUTINE TRAN3(NUC,I,INTER,N,T,IX)
160090          DIMENSION N(450),T(64,3)
160100          CALL RANDOM (IX,P)
160110          NUC=N(I)
160120          IF (P.LT.0.0)  GO TO 341
160130          IA=I+1
160140          IB=I-1
160150          IT=N(IA)+4*(N(I)-1)+16*(N(IB)-1)
160160          IF (P.GE.T(IT,1))  GO TO 341
160170          NUC=N(I)
160180          IF (NUC.EQ.1)  GO TO 31
160190          IF (NUC.EQ.2)  GO TO 32
160200          IF (NUC.EQ.3)  GO TO 33
160210          IF (P.LE.T(IT,2)) N(I)=N(I)-1
160220          IF (P.GE.T(IT,3)) N(I)=N(I)+1
160230          N(I)=N(I)-2
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160240        GO TO 341
160250     31 N(I)=N(I)+2
160260        IF (P.LE.T(IT,2)) N(I)=N(I)-1
160270        IF (P.GE.T(IT,3)) N(I)=N(I)+1
160280        GO TO 341
160290     32 N(I)=N(I)+1
160300        IF (P.LE.T(IT,2)) N(I)=N(I)-2
160310        IF (P.GE.T(IT,3)) N(I)=N(I)+1
160320        GO TO 341
160330     33 N(I)=N(I)-1
160340        IF (P.LE.T(IT,2)) N(I)=N(I)-1
160350        IF (P.GE.T(IT,3)) N(I)=N(I)+2
160360    341 CONTINUE
160370        RETURN
160380        END
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BIBLIOGRAPHY

BIBLIOGRAPHY

1. Adatugbo, Kayode, Cesar Milstein, and David S.Secher. "Molecular Anaysis of Spontaneous Somatic Mutations," Nature: 299-304, 27 June 1977.

2. Air, G.M., et al. "Gene F of Bacteriophage oX174. Correlation of Nucleotide Sequence from the DNA and Amino Acid Sequences from the Gene Product," Journal of Molecular Biology: 445-458, 1976.

3. Allfrey, Vincent G., et al. Aspects of Protein Biosynthesis. Edited by C.B. Anfinsen, Jr. New York NY: Academic Press, 1970.

4. Anfinson, Christian B. "Principles that Govern the Folding of Protein Chains," Science: 223-229, 20 July 1973.

5. Armstrong, Robert A. and Michael E. Gilpin. "Evolution in a Time-Varying Environment," Science: 591-592, 11 February 1977.

6. Arnheim, Normal and Charles E. Taylor. "Non-Darwinian Evolution: Consequences for Neutral Allelic Variation," Nature: 900-902, 30 August 1969.

7. Avery, P.J. "Extensions to the Model of an Infinate Number of Selectively Neutral Alleles in a Finite Population," Genetic Research: 145-153, 1975.

8. Ayala, Francisco J. "The Mechanisms of Evolution," Scientific American: 55-69, September 1978.

10. _____ and James W. Valentine. Evolving: The Theory and Process of Organic Evolution. Menlo Park CA: The Benjamin/Cummings Publishing Company, 1979.

11. _____ and Michael E. Gilpin. "Lack of Evidence for the Neutral Hypothesis of Protein Polymorphism: A Rejoinder," The Journal of Heredity: 377, 1974.

12. Balazs, Arthur J. and James D. Emery, Jr. Information Theory in Genetic Coding. Technical Report Wright-Patterson AFB OH: AFIT School of Engineering, May 1974.

13. Baralle, Francisco E. "Complete Nucleotide Sequence of the 5' Noncoding Region of Human Alpha- and Beta-Globin mRNA," Cell: 1085-1095, December 1977a.

14. _____. "Complete Nucleotide Sequence of the 5' Noncoding Region of Rabbit Beta- Globin mRNA," Cell: 549-558, April 1977b.

15. _____. "Structure-function Relationship of 5' Noncoding Sequences of Rabbit Alpha- and Beta-Globin mRNA," Nature: 279-281, 19 May 1977c.

16. _____ and George G. Brownlee. "AUG is the only Recognisable Signal Sequence in the 5' Noncoding Regions of Eukaryotic mRNA," Nature: 84-87, 6 July 1978.

17. Blattner, Frederic R., et al. "Charion Phages: Safer Derivatives of Bacteriophage Lambda for DNA Cloning," Science: 161-169, 8 April 1977.

18. Boyer, Samuel H. "Extraordinary Incidence of Electrophoretically Silent Genetic Polymorphisms," Nature: 443-444, 20 October 1972.

19. _____, et al. "Primate Hemoglobins: Some Sequences and Some Proposals Concerning the Character of Evolution and Mutation," Biochemical Genetics: 405-448, 1971.

20. Brimacombe, R., et al. "RNA Codewords and Protein Synthesis, VIII Nucleotide Sequence of Synonym Codons for Arginine, Valine, Cisteine, and Alanine," Proceedings of the National Academy of Science: 954-959, 1965.

21. Brown, A.H.D., D.R. Marshall, and L. Albrecht. "Profiles of Electrophoretic Alleles in Natural Populations," Genetic Research: 137-143, 1975.

22. Burns, John A. and Eugene M. Cliff. Identification of Hereditary Control Systems via Approximation Techniques. Blacksburg VA: Virginia Polytechnic Institute and State University, November 1981.

23. Buse, Gerhard. "The Present Position of Hemoglobin Research," Angewandte Chemie International Edition: 663-673, October 1971.

24. Chakraborty, Ranajit and Masatoshi Nei. "Hidden Genetic Variability within Electromorphs in Finite Populations," Genetics: 385-393, October 1976.

25. Chauvet, Jean-Pierre and Roger Acher. "Phylogeny of Hemoglobins. Beta Chain of Frog (Rana esculenta) Hemoglobin," Biochemistry: 916-927, May 1972.

26. Chernavskii, D.S. and N.M. Chernavskaya. "Some Theoretical Aspects of the Problem of Life Origin," Journal of Theoretical Biology: 13-23, 1975.

27. Chirpich, Thomas P. "Rates of Protein Evolution: A Function of Amino Acid Composition," Science: 1022-1023, 6 June 1975.

28. Clarke, Bryan. "Selective Constraints on Amino-acid Substitutions During the Evolution of Proteins," Nature: 159-160, 10 October 1970.

29. Clissold, Patricia M., Henry R.V. Arnstein, and C. James Chesterton. "Quantitation of Globin mRNA Levels during Erythroid Development in the Rabbit and Discovery of a New Beta- Related Species in Immature Erythroblasts," Cell: 353-361, June 1977.

30. Cockerham, C. Clark and Peter M. Burrows. "Selection Limits and Strategies," Proceedings of the National Academy of Science: 546-549, January 1980.

31. Conrad, Michael. "A Mechanism for the Evolution of the Genetic Code," Currents in Modern Biology: 260-269, 1970.

32. Cox, Edward C. and Charles Yanofsky. "Altered Base Ratio in the DNA of an Escherichia coli Mutator Strain," Proceedings of the National Academy of Science: 1895-1902, 1967.

33. Crick, F.H.C. "The Genetic Code--Yesterday, Today, and Tomorrow," Cold Springs Harbor Symposia on Quantitative Biology: 1-9, 1966.

34. _____ and A. Klug. "Kinky Helix," Nature: 530-532, 12 June 1975.

35. _____. "Origin of the Genetic Code," Nature: 119, 14 January 1967.

36. Crow, James F. "The Dilemma of Mearly Meutral Mutations: How Important are they for Evolution and Human Welfare?" Journal of Heredity: 306-316, 1972.

37. Curtis, Peter J. et al. "Presence of a Putative 15S Precursor to Beta-Globin m-RNA but not to Alpha-Globin m-RNA in Friend Cells," Proceedings of the National Academy of Science: 3184-3188, August 1977.

38. Dayhoff, Margaret O., Editor. Atlas of Protein Sequence and Structure, Volume 5. Silver Springs MD: The National Biomedical Research Foundation, 1972.

39. _____. Atlas of Protein Sequence and Structure, Volume 5, Supplement 1. Silver Springs MD: The National Biomedical Research Foundation, 1973.

40. _____. Atlas of Protein Sequence and Structure, Volume 5, Supplement 2. Silver Springs MD: The National Biomedical Research Foundation, 1976.

41. _____. Atlas of Protein Sequence and Structure, Volume 5, Supplement 3. Silver Springs MD: The National Biomedical Research Foundation, 1978.

42. Demoulin, Vincent. "Protein and Nucleic Acid Sequence Data and Phylogeny," Science: 1036-1038, 7 September 1979.

43. Dickerson, Richard E. "Chemical Evolution and the Origin of Life," Scientific American: 70-86, September 1978.

44. Dillon, Lawrence S. The Genetic Mechanism and the Origin of Life. New York NY: Plenum Press, 1978.

45. Dunnill, Peter. "Triplet Nucleotide-Amino-Acid Pairing; a Stereochemical Basis for the Division between Protein and Non-Protein Amino-Acids," Nature: 1267-1268, 18 June 1966.

46. Efstratiadis, Argiris, Fotis C. Kafatos, and Tom Maniatis. "The Primary Structure of Rabbit B-Globin mRNA as Determined from Cloned DNA," Cell: 571-585, April 1977.

47. Egbert, Larre N. "Isolation of the Intact Strands of the Deoxyribonucleic Acid of TO3; A Bacteriophage for Bacillus stearothermophilus," Biochimica et Biophkysica Acta: 310-318, 1972.

48. Epstein, Charles J. "Non-Randomness of Amino-Acid Changes in the Evolution of Homologous Proteins," Nature: 355-359, 22 July 1967.

49. _____. "Relation of Protein Evolution to Tertiary Structure," Nature: 203, 26 September 1964.

50. _____. "Role of Amino-Acid 'Code' and of Selection for Conformation in the Evolution of Proteins," Nature: 25-28, 2 April 1966.

51. Ewens, W.J. and J.H. Gillespie. "Statistical Results for the Neutral Allele Model," MRC Technical Summary Report: 1372, March 1974.

52. Felsenstein, Joseph. A Likelihood Approach to Character Weighting and What it Tells Us About Parsimony and Compatibility. Seattle WA: University of Washington, September 1981a.

53. _____. Evolutionary Trees from DNA Sequences: A Maximum-Likelihood Approach. Seattle WA: University of Washington, September 1981b.

54. _____. The Statistical Inference Approach to Inferring Evolutionary Trees and What it Tells Us About Parsimony and Compatibility. Seattle WA: University of Washington, September 1981c.

55. _____. Theoretical Studies of Speciation and Evolutionary Inference. Seattle WA: University of Washington, September 1981d.

56. _____, Stanley A. Sawyer, and Rochelle Kochin. An Efficient Method for Matching Nucleic Acid Sequences. Seattle WA: University of Washington, September 1981.

57. Fiddes, John C. "The Nucleotide Sequence of a Viral DNA," Scientific American: 55-67, December 1977.

58. Fiers, W., et al. "Complete Nucleotide Sequence of Bacteriophage MS2 RNA: Primary and Secondary Structure of the Replicase Gene," Nature: 500-507, 8 April 1976.

59. Fitch, Walter M. "Evidence Suggesting a Non-Random Character to Nucleotide Replacements in Naturally Occurring Mutations," Journal of Molecular Biology: 499-507, 1967.

60. _____. "Is their Selection Against Wobble in Codon-Anticodon Pairing?" Science: 1173-174, 10 December 1976.

61. _____ and Emanuel Margoliash. "The Usefulness of Amino Acid and Nucleotide Sequences in Evolutionary Study," Evolutionary Biology, Volume 4, Edited by Theodosius Dobzhansky, Max K. Hecht, and William C. Steere. New York NY: Appleton Century-Crofts, 1970.

62. _____ and Etan Markowitz. "An Improved Method for Determining Codon Variability in a Gene and Its Application to the Rate of Fixation of Mutations in Evolution," Biochemical Genetics: 579-593, 1970.

63. Fluendy, Malcolm. "Monte Carlo Methods," Markov Chains and Monte Carlo Calculations in Polymer Science, Edited by George G. Lowry. New York NY: Marcel Dekker, Inc., 1970.

64. Fogel, Lawrence J., Alvin J. Owins, and Michael J. Walsh. Artificial Intelligence Through Simulated Evolution. New York NY: John Wiley and Sons, Inc., 1966.

65. Fox, Sidney W. "Origins of Biological Information and the Genetic Code," Molecular and Cellular Biochemistry: 129-142, 15 April 1974.

66. Freese, Ernst and Akira Yoshida. "The Role of Mutations in Evolution," Science: 341-355, 28 January 1977.

67. Fuerst, Paul A, Ranajit Chakaborty, and Masatoshi Nei. "Statistical Studies on Protein Polymorphism in Natural Populations I. Distribution of Single Locus Heterozygosity," Genetics: 455-483, June 1977.

68. Gautier, C. "Average Proteins and the Genetic Code," Science: 642, 5 November 1976.

69. Georgiev, G.P., et al. "Isolation of Eukaryotic DNA Fragments Containing Structural Genes and the Adjacent Sequences," Science: 394-397, 28 January 1977.

70. _____, et al. "On the Structure of Transcriptional Unit in Mamalian Cells," Biochimica et Biophysica Acta: 259-283, 1972.

71. Geracitano, R. and F. Persico. "A Model for the Stabilization of the Genetic Information by the Interaction Between Superimposed Base-Pairs," Physiological Chemistry and Physics: 361-370, 1971.

72. Gilbert, Walter. "Why Genes in Pieces," Nature: 501-502, 9 February 1978.

73. Gillespie, David. "Newly Evolved Repeated DNA Sequences in Primates," Science: 889-891, 20 March 1977.

74. Gilman, John G. "Comparative Sequence Data on Adult Major and Minor Beta Chains for Two Species, Mus musculus and Mus cervicolor," Biochemistry Journal: 43-55, 1976.

75. Goldberg, Alfred L. and Robert E. Wittes. "Genetic Code: Aspects of Organization," Science: 420-422, 22 July 1966.

76. Goodman, Morris et al. "Molecular Evolution in the Descent of Man," Nature: 604-613, 29 October 1971.

77. Goossens, Michel et al. "Triplicated Alpha-Globin Loci in Humans," Proceedings of the National Academy of Science: 518-521, January 1980.

78. Grantham, R. "Amino Acid Difference Formula to Help Explain Protein Evolution," Science: 862-864, 6 September 1974.

79. Harbers, Klaus and John H. Spencer. "Nucleotide Clusters in Deoxyribonucleic Acids. Pyrimidine Oligonucleotides of Mouse L-Cell Satellite Deoxyribonucleic Acid and Main-Band Deoxyribonucleic Acid," Biochemistry: 1094-1101, June 1974.

80. Harper, Charles W., Jr. "Origin of Species in Geologic Time: Alternatives to the Eldridge-Gould Model," Science: 47-48, 3 October 1975.

81. Hartman, Hyman. "Speculations on the Evolution of the Genetic Code," Orgins of Life: 423-427, 1975.

82. Hasegawa, Masami and Taka-aki Yano. "Entropy of the Genetic Information and Evolution," Orgins of Life: 219-227, 1975.

83. Hinegardner, Ralph. "Evolution of Cellular DNA content in Teleost Fishes," American Naturalist: 517-523, November-December 1968.

84. _____ and Joseph Engelberg. "Rationale for a Universal Genetic Code," Science: 1083-1085, 22 November 1963.

85. Holmquist, Richard. "Beta-Galactosidase and Selective Neutrality," Science: 1012-1014, 9 March 1979.

86. ____, et al. "The Evolution of the Globin Family Genes: Concordance of Stochastic and Augmented Maximum Parsimony Genetic Distances for Alpha-Hemoglobin, Beta-Hemoglobin and Myoglobin Phylogenies," Journal of Molecular Biology: 39-74, 1976.

87. _____ Thomas H. Jukes, and Sharon Pangburn. "Evolution of Transfer RNA," Journal of Molecular Biology: 91-116, 1973.

88. Holness, N. John and Gladys Atfield. "The Nucleotide Sequence of Cysteine Transfer Ribonucleic Acid from Bakers' Yeast," Biochemistry Journal: 447-454, 1976.

89. Hopfield, J.J. "Origin of the Genetic Code: A Testable Hypothesis Based on t-RNA Structure, Sequence, and Kinetic Proofreading," Proceedings of the National Academy of Science: 4334-4338, September 1978.

90. Hori, Hiroshi and Syozo Osawa. "Evolutionary change in 5S RNA Secondary Structure and a Phylogenic Tree of 54 5S RNA Species," Proceedings of the National Academy of Science: 381-385, January 1979.

91. Hutton, James R. and James G. Wetmur. "Effect of Chemical Modification on the Rate of Renaturation of Deoxyribonucleic Acid. Deaminated and Glyoxalated Deoxyribonucleic Acid," Biochemistry: 558-563, March 1973.

92. Ingram, Vernon M. The Hemoglobins in Genetics and Evolution. New York NY: Columbia University Press, 1963.

93. _____ and Emelie Sullivan. "Amino Acids in Yeast Acceptor Ribonucleic Acid," Biochimica et Biophysica Acta: 583-587, 1962.

94. Josse, John, A.D. Kaiser, and Arthur Kornberg. "Enzymatic Synthesis of Deoxyribonucleic Acid VIII. Frequencies of Nearest Neighbor Base Sequences in Deoxyribonucleic Acid," Journal of Biological Chemistry: 864-875, March 1961.

95. Jukes, Thomas H. "Arginine as an Evolutionary Intruder into Protein Synthesis," Biochemical and Biophysical Research Communications: 709-714, 1973a.

96. _____. "How Many Anticodons?" Science: 319-320, 21 October 1977.

97. _____. "Possibilities for the Evolution of the Genetic Code from a Preceding Form," Nature: 22-26, 2 November 1973b.

98. _____, et al. "Amino Acid Composition of Proteins: Selection Against the Genetic Code," Science: 50-51, 4 July 1975.

99. _____ and Richard Holmquist. "Evolutionary Clock: Nonconstancy of rate in Different Species," Science: 530-532, 11 August 1972.

100. _____, Richard Holmquest, and Herbert Moise. "Average Protein and the Genetic Code: A Rejoinder," Science: 642-643, 5 November 1976.

101. Jumarie, Guy. "Structural Entropy, Information Potential, Information Balance and Evolution in Self-organizing Systems," International Journal of Systems Science: 953-972, 1974.

102. Jungck, John R. "Pre-Darwinian and Non-Darwinian Evolution of Proteins," Currents in Modern Biology: 307-318, 1971.

103. Kassell, Beatrice. "Protein Inhibitors of Non-proteolytic Enzymes," Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, Volume 5, Edited by Boris Weinstein. New York NY: Marcel Dekkar, Inc., 1978.

104. Keosian, John. "Life's Beginnings--Origin of Evolution?" Origins of Life: 285-293, 1974.

105. Kharchenko, E.P. "Evolution of Nucleotide Composition of DNA: First Hypothesis and New Facts," Journal of Evolutionary Biochemistry and Physiology: 30-34, 1975.

106. Kimura, Motoo. "Average Time until Fixation of a Mutant Allele in a Finite Population under Continued Mutation Pressure: Studies by Analytical, Numerical, and Pseudo-Sampling Methods," Proceedings of the National Academy of Science: 522-526, January 1980.

107. _____. Diffusion Models in Population Genetics. London, England: Methuen and Company, Ltd., 1964.

108. _____. "Evolutionary Rate at the Molecualr Level," Nature: 624-626, 17 February 1968.

109. _____. "Model of Effectively Neutral Mutations in which Selective Constraint is Incorporated," Proceedings of the National Academy of Science: 3440-3444, July 1979a.

110. _____. "The Neutral Theory of Molecular Evolution," Scientific American: 98-126, November 1979b.

111. _____. "The Rate of Molecular Evolution Considered from the Standpoint of Population Genetics," Proceedings of the National Academy of Science: 1181-1188, 1969.

112. _____ and Tomoko Ohta. "Distribution of Allelic Frequencies in a Finite Pcpulation under Stepwise Production of Neutral Alleles," Proceedings of the National Academy of Science: 2761-2769, July 1975.

113. _____ and Tomoko Ohta. "On Some Principles Governing Molecular Evolution," Proceedings of the National Academy of Science: 2848-2852, July 1974.

114. _____ and Tomoko Ohta. "Protein Polymorphism as a Phase of Molecular Evolution," Nature: 467-469, 12 February 1971a.

115. _____ and Tomoko Ohta. Theoretical Aspects of Population Genetics. Princeton NJ: Princeton University Press, 1971b.

116. King, Jack Lester and Thomas H. Jukes. "Non-Darwinian Evolution," Science: 788-798, 16 May 1969.

117. King, Mary-Claire and A.C. Wilson. "Evolution at Two-Levels in Humans and Chimpanzees," Science: 107-116, 11 April 1975.

118. Kingman, J.F.C. "A Note of Multidimensional Models of Neutral Mutation," Theoretical Population Biology: 285-290, 1977.

119. Kisselev, Oley I., Vladimir S. Gaitskhoki, and Solomon A. Neifakh. "On the Transfer of Nuclear RNA into Isolated Mitrochondria. Further Evidence for Template Properties of Nuclear RNA Taken up by Isolated Mitrochondria," Molecular and Cellular Biochemistry: 149-153, 28 February 1975.

120. Klotz, Lynn C., et al. "Calculation of Evolutionary Trees from Sequence Data," Proceedings of the National Academy of Science: 4516-4520, September 1979.

121. Knapp, Gayle, et al. "Transcription and Processing of Intervening Sequences in Yeast tRNA Genes," Cell: 221-236, June 1978.

122. Koch, Robert E. "The Influence of Neighboring Base Pairs upon Base-Pair Substitution Mutation Rates," Proceedings of the National Academy of Science: 773-776, April 1971.

123. Lacey, James C., Arthur L. Weber and William E. White, Jr. "A Model for the Coevolution of the Genetic Code and the Process of Protein Synthesis: Review and Assessment," Origins of Life: 273-283, 1975.

124. Lagerkvist, Ulf. "Codon Misreading: A Restriction Operative in the Evolution of the Genetic Code," American Scientist: 192-198, March-April 1980.

125. Lasettre, Edwin N. and John P. Howe. "Thermodynamic Properties of Binary Solid Solutions for the Basis of the Nearest Neighbor Approximation," Journal of Chemical Physics: 747-754, October 1941.

126. Latter, B.D.H. "Enzyme Polymorphisms: Gene Frequency Distributions with Mutation and Selection for Optimal Activity," Genetics: 325-331, February 1975.

127. Lewontin, R.C. and J.L. Hubby. "A Molecular Approach to the Study of Genic Heterozygosity in Natural Populations," Genetics: 595-609, August 1966.

128. _____, L.R. Ginzburg, and S.D. Tuljapurkar. "Heterosis as an Explanation for Large Amounts of Genic Polymorphism," Genetics: 149-1[illegible], January 1978.

129. Li, Wen-Hsiung. "A Mixed Model of Mutation from Electrophoretic Identity of Proteins within and between Populations," Genetics: 423-432, June 1976a.

130. _____. "Electrophoretic Identity of Proteins in a Finite Population and Genetic Distance between Taxa," Genetic Research: 119-127, October 1976b.

131. _____. "Maintenance of Genetic Variability under Mutation and Selection Pressure in a Finite Population," Proceedings of the National Academy of Science: 2509-2513, June 1972.

132. Lowry, George G. "Introduction: Deterministic and Stochastic Approaches," Markov Chains and Monte Carlo Calculations in Polymer Science, Edited by George G. Lowry. New York NY: Marcel Dekker, Inc., 1970.

133. Mackay, A.L. "Optimization of the Genetic Code," Nature: 159-160, 14 October 1967.

134. Margoliash, E. "The Molecular variations of Cytochrome c as a Function of the Evolution Species," Membranes, Dissipative Structures and Evolution, Volume XXIX, Edited by G. Nicolis and R. Lefever. New York NY: John Wiley and Sons, Inc., 1975.

135. Marmur, J. and P. Doty. "Determination of the Base Composition of Deoxyribonucleic Acid from its Thermal Decomposition Temperature," Journal of Molecular Biology: 109-118, 1962.

136. Marotta, Charles A., et al. "Human Beta-Globin Messenger RNA III. Nucleotide Sequences Derived from Complementary DNA," Journal of Biological Chemistry: 5040-5051, July 1977.

137. Maruyama, Takeo and Motoo Kimura. "Theoretical Study of Genetic Variability, Assuming Stepwise Production of Neutral and Very Slightly Deleterious Mutations," Proceedings of the National Academy of Science: 919-922, February 1978.

138. Mayr, Ernst. "Evolution," Scientific American: 47-55, September 1978.

139. _____. Populations, Species, and Evolution: An Abridgement of "Animal Species and Evolution". Cambridge MA: The Belknap Press of Havard University Press, 1970.

140. Maxin, A.Z. "Evolution of DNA Structure: Direction, Mechanism, Rate," Journal of Molecular Biology: 203-220, 1975.

141. Mazur, Jacob. "Higher Order Markov Chains and Statistical Thermodynamics of Linear Polymers," Markov Chains and Monte Carlo Calculations in Polymer Science, Edited by George G. Lowry. New York NY: Marcel Dekker, Inc., 1970.

142. Melcher, Gerhard. "A New Hypothesis on the Evolution of the Genetic Code," Biophysik: 25-28, 1970.

143. Mikelsaar, H.N. "A Concept of Amino Acid Archaeorelation: Orgin of Life and the Genetic Code," Journal of Theoretical Biology: 203-212, 1975.

144. Montroll, Elliott W. "Statistical Mechanics of Nearest Neighbor Systems," Journal of Chemical Physics: 706-721, September 1941.

145. Moore, G. William, John Barnabas, and Morris Goodman. "A Method for Constructing Maximum Parsimony Ancestral Amino Acid Sequences on a Given Network," Journal of Theoretical Biology: 459-485, 1973.

146. _____, et al. "Stochastic versus Augmented Maximum Parsimony Method for Estimating Superimposed Mutations in the Divergent Evolution of Protein Sequences. Methods Tested on Cytochrome c Amino Acid Sequences," Journal of Molecular Biology: 15-37, 1976.

147. Moran, P.A.P. "Wandering Distributions and the Electrophoretic Profiles," Theoretical Population Biology: 145-149, 1976.

148. Morgan, Philip "Frequency Dependent Selection at Two Enzyme Loci in Drosophila melangaster," Nature: 765-766, 28 October 1976.

149. Mukai, Terumi and C. Clark Cockerham. "Spontaneous Mutation Rates at Enzyme Loci in Drosphila melangaster," Proceedings of the National Academy of Science: 2514-2517, June 1977.

150. Mullins, W.W. "Analysis of the Linear Cooperative Problem as a Markoff Process," The Physical Review: 389-393, 15 April 1959.

151. Myhre, Janet M. "Markov Chains," Markov Chain and Monte Carlo Calculations in Polymer Science, Edited by George G. Lowry. New York NY: Marcel Dekker, Inc., 1970.

152. Nagyvary, Joseph and Jamos H. Fendler. "Origin of the Genetic Code: A Physical-Chemical Model of Primative Codon Assignment," Origins of Life: 357-362, 1974.

153. Nakishima, Tadayoshi and Sidney W. Fox. "Selective Condensation of Amino-acyl Adenylates by Nucleoproteinoid Microparticles," Proceedings of the National Academy of Science: 106-108, January 1972.

154. Neel, James V. "'Private' Genetic Variants and the Frequency of Mutation Among South American Indians," Proceedings of the National Academy of Science: 3311-3315, December 1977.

155. _____ and Edward D. Rothman. "Indirect Estimates of Mutation Rates in Tribal Amerindians," Proceedings of the National Academy of Science: 5585-5588, November 1978.

156. Nienhuis, Arthur W. and H. Franklin Bunn. "Hemoglobin Switching in Sheep and Goats: Occurrence of Hemoglobins A and C in the Same Red Cell," Science: 946-948, 13 September 1974.

157. Nirenberg, M., et al. "RNA Codewords and Protein Synthesis," Proceedings of the National Academy of Science: 1161-1168, 1965.

158. _____, et al. "The RNA Code and Protein Synthesis," Cold Springs Harbor Symposia on Quantitative Biology: 11-24, 1966.

159. O'Brien, Stephen J. and Ross J. MacIntyre. "An Analysis of Gene-Enzyme Variability in Natural Populations of Drosophila melangaster and D. simulins," American Naturalist: 97-113, March-April 1969.

160. Ohno, Susumu. "Ancient Linkage Groups and Frozen Accidents," Nature: 259-262, 3 August 1973.

161. Ohta, Tomoko. "Mutational Pressure as the Main Cause of Molecular Evolution and Polymorphism," Nature: 351-354, 29 November 1974.

162. _____. "Role of Very Slightly Deleterious Mutations in Molecular Evolution and Polymorphism," Theoretical Population Biology: 254-275, 1976.

163. _____. "Statistical Analysis of Drosophila and Human Protein Polymorphism," Proceedings of the National Academy of Science: 3194-3196, August 1975.

164. _____ and Motoo Kimura. "Amino Acid Composition of Proteins as a Product of Molecular Evolution," Science: 150-153, 8 October 1971.

165. _____ and Motoo Kimura. "Statistical Analysis of the Base Composition of Genes Using Data on the Amino Acid Composition of Proteins," Genetics: 387-395, March-April 1970.

166. _____ and Motoo Kimura. "Theoretical Analysis of Electrophoretically Detectable Polymorphisms: Models of Very Slightly Deleterious Mutations," American Naturalist: 137-145, 1975.

167. Okada, Yoshimi, et al. "Molecular Basis of a Mutational Hot Spot in the Lysozyme Gene of Bacteriophage T4," Nature: 338-341, 14 April 1972.

168. Olson, Wilma K. "Configurational Statistics of Polynucleotide Chains. An Updated Virtual Bond Model to Treat Effects of Base Stacking," Macromolecules: 721-728, 1980.

169. Oppenheim, Irwin, Kurt E. Shuler, and George H. Weiss. Stochastic Processes in Chemical Physics: The Master Equation. Cambridge MA: The MIT Press, 1977.

170. Orgel, L.E. "A Possible Step in the Origin of the Genetic Code," Israel Journal of Chemistry: 287-292, 1972.

171. Papentin, Frank. "A Darwinian Evolutionary System," Journal of Theoretical Biology: 417-430, 1973.

172. Pelc, S.R. and M.G.E. Welton. "Stereochemical Relationship Between Coding Triplets and Amino-Acids," Nature: 868-870, 26 February 1966.

173. Peller, Leonard. "Thermodynamic Considerations in the Synthesis and Assembly of Biological Macromolecules," Macromolecules: 609-615, 1980.

174. Perutz, M.F. and H. Lehmann. "Molecular Pathology of Human Haemoglobin," Nature: 902-909, 31 August 1968.

175. _____, et al. "Three-Dimensional Fourier Synthesis of Horse Oxyhaemoglobin at 2.8 A Resolution: The Atomic Model," Nature: 131-139, 13 July 1968.

176. Pivec, L., J. Stokrova and Z. Sormova. "Primordal Heterogeneity of Base Composition of Calf Thymus Data," Biochemica et Biophysica Acta: 179-190, 1972.

177. Polya, Gidean M. and D.R. Phillips. "The Occurrence in Amino Acid Sequences of Extensive Informational Symmetries Based on Possible Codon-Codon Complementarity in the Encoding Polynucleotides," Biochemistry Journal: 681-690, 1976.

178. Popp, Raymond A. and Eddie G. Bailiff. "Sequence of Amino Acids in the Major and Minor Beta-Chains of the Diffuse Hemoglobin from BALB/c Mice," Biochemica et Biophysica Acta: 61-67, 73.

179. Price, Peter M., James H. Conover, and Kurt Hirschorn. "Radiographic Taging of Metaphase Chromosomes with RNA for the Beta, Alpha, and Sigma Hemoglobin Chains," Nature: 340-342, 9 June 1972.

180. Proudfoot, Nicholas J. "Complete 3' Noncoding Region Sequences of Rabbit and Human Beta- Globin Messinger RNAs," Cell: 559-570, April 1977.

181. Reanney, D.C. "Origin of the Genetic Code," Mauri Ora: 45-58, 1974.

182. Reddy, V.B., et al. "The Genome of Simian Virus 40," Science: 494-502, 5 May 1978.

183. Rein, Robert and Frank E. Harris. "Studies of Hydrogen-Bonded Systems IV. Radiation-Induced Tunneling and Tautomeric Equilibria in Guanine-Cytosine Base Pair," The Journal of Chemical Physics: 1797-1799, 1 September 196[illegible].

184. Renger, Hartmut C. and Claudio Basilico. "Mutation Causing Temperature-Sensative Expression of Cell Transformation by a Tumor Virus," Proceedings of the National Academy of Science: 109-114, January 1972.

185. Ricard, Bernice and Winston Salser. "Secondary Structures formed by Random RNA Sequences," Biochemical and Biophysical Research Communications: 548-554, March 1975.

186. Richmond, Rollin C. "Non-Darwinian Evolution: A Critique," Nature: 1025-1028, 14 March 1970.

187. Rifkin, D.B., et al. "Possible Ambiguity in the Coding of Mouse Hemoglobin," Cold Springs Harbor Symposia on Quantitative Biology: 715-718, 1966.

188. Robertus, J.D., et al. "Structure of Yeast Phenylalanine tRNA at 3 A Resolution," Nature: 546-551, 16 August 1974.

189. Rothman, Edward D. and Julian Adams. "Estimation of Expected Number of Rare Alleles of a Locus and Calculation of Mutation Rate," Proceedings of the National Academy of Science: 5094-5098, October 1978.

190. Rudner, Rivka and Mary LeDoux. "Distribution of Pyrimidined Oligonucleotides in Complementary Strand Fractions of Escherichia coli Deoxyribonucleic Acid," Biochemistry: 118-125, January 1974.

191. Samson, Leona and John Cairns. "A New Pathway for DNA Repair in Escherichia coli," Nature: 281-283, 19 May 1977.

192. Sanger, F., et al. "Nucleotide Sequence of Bacteriophage OX174 DNA," Nature: 687-695, 24 February 1977.

193. Sarich, V.M. and A.C. Wilson. "Rates of Albumin Evolution in Primates," Proceedings of the National Academy of Science: 142-148, 1967.

194. Saunders, Grady F., et al. "Populations of Repeated DNA Sequences in the Human Genome," Journal of Molecular Biology: 323-334, 1972.

195. Schaap, Tamar. "Dual Information in DNA and the Evolution of the Genetic Code," Journal of Theoretical Biology: 293-298, 1971.

196. Schimmel, Paul R., et al. "Molecular Dissection of an Enzyme that Recognize Transfer RNA," Macromolecules: 716-721, 1980.

197. Schwartz, Robert M. and Margaret O. Dayhoff. "Orgin of Prokaryotes, Eukaryotes, Mitochondrial, and Chloroplasts," Science: 395-403, 27 January 1978.

198. _____ and Margaret O. Dayhoff. "Protein and Nucleic Acid Sequence Data and Phylogeny," Science: 1038-1039, 7 September 1979.

199. Sciliano, Michael J., Mary R. Bordelon, and Peter O. Kohler. "Expression of Human Adenosine Deaminase after Fusion of Adenosine Deaminase Deficient Cells with Mouse Fibroblast," Proceedings of the National Academy of Science: 936-940, February 1978.

200. Selander, Robert K., W. Grainge Hunt, and Sah Y. Yang. "Protein Polymorphism and Genic Heterozygosity in Two European Subspecies of the House Mouse," Evolution: 379-390, September 1969.

201. _____, et al. "Genetic Variations in the Horseshoe Crab(Linnulus polyphamus), a Phylogenetic 'Relic'," Evolution: 402-414, June 1970.

202. Sellers, Peter H. "Pattern Recognition in Genetic Sequences," Proceedings of the National Academy of Science: 3041-3045, July 1979.

203. Sick, K., et al. "Haemoglobin G-Copenhagen and Haemoglobin J-Cambridge. Two New B-Chain Variants of Haemoglobin A," Biochimica et Biophysica Acta: 231-242, 1967.

204. Siminovitch, Louis. "On the Nature of Hereditable Variation in Cultured Somatic Cells," Cell: 1-11, January 1976.

205. Smith, Hamilton O. "Nucleotide Sequence Specificity of Restriction Endonucleases," Science: 455-461, 3 August 1979.

206. Smith, J.D. "Genetic and Structural Analysis of Transfer RNA," British Medical Bulletin: 220-225, 1973.

207. Smith, J. Maynard. "'Haldane's Dilemma' and the Rate of Evolution," Nature: 219, 14 September 1968.

208. Smithies, Oliver, et al. "Cloning Human Fetal Sigma Globin and Mouse Alpha-Type Globin DNA: Characterization and Partial Sequencing," Science: 1284-1289, 22 December 1978.

209. Soil, Dieter. "Enzymatic Modification of Transfer RNA," Science: 293-299, 23 July 1971.

210. Sonneborn, T.M. "Degeneracy of the Genetic Code: Extent, Nature, and Genetic Implications," Evolving Genes and Proteins, Edited by V. Bryson and N.J. Vogel. New York NY: Academic Press, 1965.

211. Speyer, Joseph F. "Mutagenic DNA Polymerase," Biochemical and Biophysical Research Communications: 6-8, 1965.

212. Stansfield, William D. Schaum's Outline of Theory and Problems of Genetics. New York NY: Mcgraw-Hill Book Company, 1969.

213. Stebbins, G. Ledyard. Processes of Organic Evolution. Englewood Cliffs, NJ: Prentice-Hall, Inc., 1977.

214. Stretton, A.O.W. "The Genetic Code," British Medical Bulletin: 229-235, 1965.

215. Strinivasan, P.R. and Ernest Borek. "Enzymatic Alteration of Nucleic Acid Structure," Science: 548-553, 7 August 1964.

216. Stryer, Lubert. Biochemistry. San Fransico CA: W.H. Freeman and Company, 1975.

217. Subak-Sharpe, H.,Wilma M. Shepherd, and J. Hay. "Studies on sRNA Coded by Herpes Virus," Cold Springs Harbor Symposia on Quantitative Biology: 583-594, 1966.

218. Sueoka, Noboru. "On the Genetic Basis of Variation and Heterogeniety of DNA Base Composition," Proceedings of the National Academy of Science: 582-592, 1962.

219. Sutton, W.D. and P.M.B. Walker. "Self-Renaturing Fractions in the Separated Strands of Mouse Satellite Deoxyribonucleic Acid," Biochemistry Journal: 193-198, 1972.

220. Sved, J.A. "Possible Rates of Gene Substitution in Evolution," American Naturalist: 283-293, 1968.

221. Swartz, M.N., T.A. Trautner, and Arthur Kornberg. "Enzymatic Synthesis of Deoxyribonucleic Acid I. Further Studies on Nearest Neighbor Base Sequences in Deoxyribonucleic Acids," Journal of Biological Chemistry: 1961-1967, June 1962.

222. Thomas, B.R. "The tRNA - mRNA Complex of Protein Biosynthesis," Biochimie: 1325-1339, 1973.

223. Thompson, E.A. and J.V. Neel. "Probability of Founder Effect in a Tribal Population," Proceedings of the National Academy of Science: 1442-1445, March 1978.

224. Tiemeier, David C., et al. "A Comparison of Two Cloned Mouse Beta-Globin Genes and their Surrounding and Intervening Sequences," Cell: 237-245, June 1978.

225. Tilghman, Shirley M., et al. "The Intervening Sequence of a Mouse Beta-Globin Gene is Transcribed within the 15S Beta-Globin m-RNA Precurser," Proceedings of the National Academy of Science: 1309-1313, March 1978a.

226. _____, et al. "Intervening Sequence of DNA Identified in the Structured Portion of Mouse Beta-Globin Gene," Proceedings of the National Academy of Science: 725-729, February 1978b.

227. Tonegawa, Susumu, et al. "Sequence of a Mouse Germ-Line Gene for a Variable Region of an Immunoglobin Light Chain," Proceedings of the National Academy of Science: 1485-1489, March 1978.

228. Trautner, T.A., M.N. Swartz, and Arthur Kornberg. "Enzymatic Synthesis of Deoxyribonucleic Acid X. Influence of Bromouracil Substitutions on Replication," Proceedings of the National Academy of Science: 449-455, 1962.

229. Ullman, John S. and Brian J. McCarthy. "The Relationship Between Mismatched Base Pairs and the Thermal Stability of DNA Duplexes I. Effects of Depurination and Chain Scission," Biochemica et Biophysica Acta: 405-415, 1973.

230. Van den Berg, Johan, et al. "Comparison of cloned Rabbit and Mouse B-Globin Genes Showing Strong Evolutionary Divergence of Two Homologous Pairs of Introns," Nature: 37-44, 2 November 1978.

231. Vann, Edwin. "The Effects of Various Homologous Chromosomes on the Viability of Drosophila melanogaster Lethal Heterozygotes," American Naturalists: 401-404, July-August 1970.

232. Waehneldt, Thomas Voind, and Sidney W. Fox. "The Binding of Basic Proteinoids with Organismic or Thermally Synthesized Polynucleotides," Biochimica et Biophysica Acta: 239-245, 1968.

233. Walker, G.W.R. "An Analytical Study of the Origin of the Genetic Code," Proceedings International Symposia on Uptake of Informative Molecules by Living Cells, Edited by L. Ledoux. London, United Kingdom: North Holland, 1970.

234. _____. "Genetics and the Origin of the Genetic Code," Origins of Life: 351-356, 1974.

235. Walker, P.M.B. "How Different are the DNAs from Related Animals?" Nature: 228-232, 20 July 1968.

236. Watson, J.D. Molecular Biology of the Gene. New York NY: W.A. Benjamin, Inc., 1965.

237. Wehrhahn, C.F. "The Evolution of Selectively Similar Electrophoretically Detectable Alleles in Finite Natural Populations," Genetics: 375-394, June 1975.

238. Weinstein, I. Bernard. "Comparative Studies on the Genetic Code," Cold Springs Symposia on Quantitative Biology: 579-580, 1963.

239. Weir, B.S., A.H.D. Brown, and D.R. Marshall. "Testing for Selective Neutrality of Electrophoretically Detectable Protein Polymorphisms," Genetics: 639-659, November 1976.

240. Welton, M.G.E. and S.R. Pelc. "Specificity of the Stereochemical Relationships between Ribonucleic Acid Triplets and Amino-Acids," Nature: 870-872, 26 February 1966.

241. White, Harold B. III, Brian E. Laux, and Don Dennis. "Messenger RNA Structure Compatibility of Hairpin Loops with Protein Sequence," Science: 1264-1266, 17 March 1972.

242. Williamson, Bob. "DNA Insertion and Gene Structure," Nature: 295-297, 24 November 1977.

243. Windwer, Stanley. "Polymer Conformation and the Excluded-Volume Problem," Markov Chain and Monte Carlo Calculation in Polymer Sciences, Edited by George G. Lowry. New York NY: Marcel Dekker, Inc., 1970.

244. Woese, Carl R. "Models for the Evolution of Codon Assignments," Journal of Molecular Biology: 235-240, 1969.

245. _____. "Nature of the Biological Code," Nature: 217, 23 June 1962.

246. _____. "On the Evolution of the Genetic Code," Proceedings of the National Academy of Science: 1546-1551, 1965.

247. _____. "Universality in the Genetic Code," Science: 1030-1031, 22 May 1964.

248. Wong, J. Tze-Fei. "Role of Minimization of Chemical Differences between Amino Acids in the Evolution of the Genetic Code," Proceedings of the National Academy of Science: 1083-1086, February 1980.

249. Yamazaki, Tsuneyaki and Takeo Maruyama. "Evidence for the Neutral Hypothesis of Protein Polymorphism," Science: 56-58, 6 October 1972.

250. Yockey, Hubert P. "An Aplication of Information Theory to the Central Dogma and the Sequence Hypothesis," Journal of Theoretical Biology: 369-406, 1974.

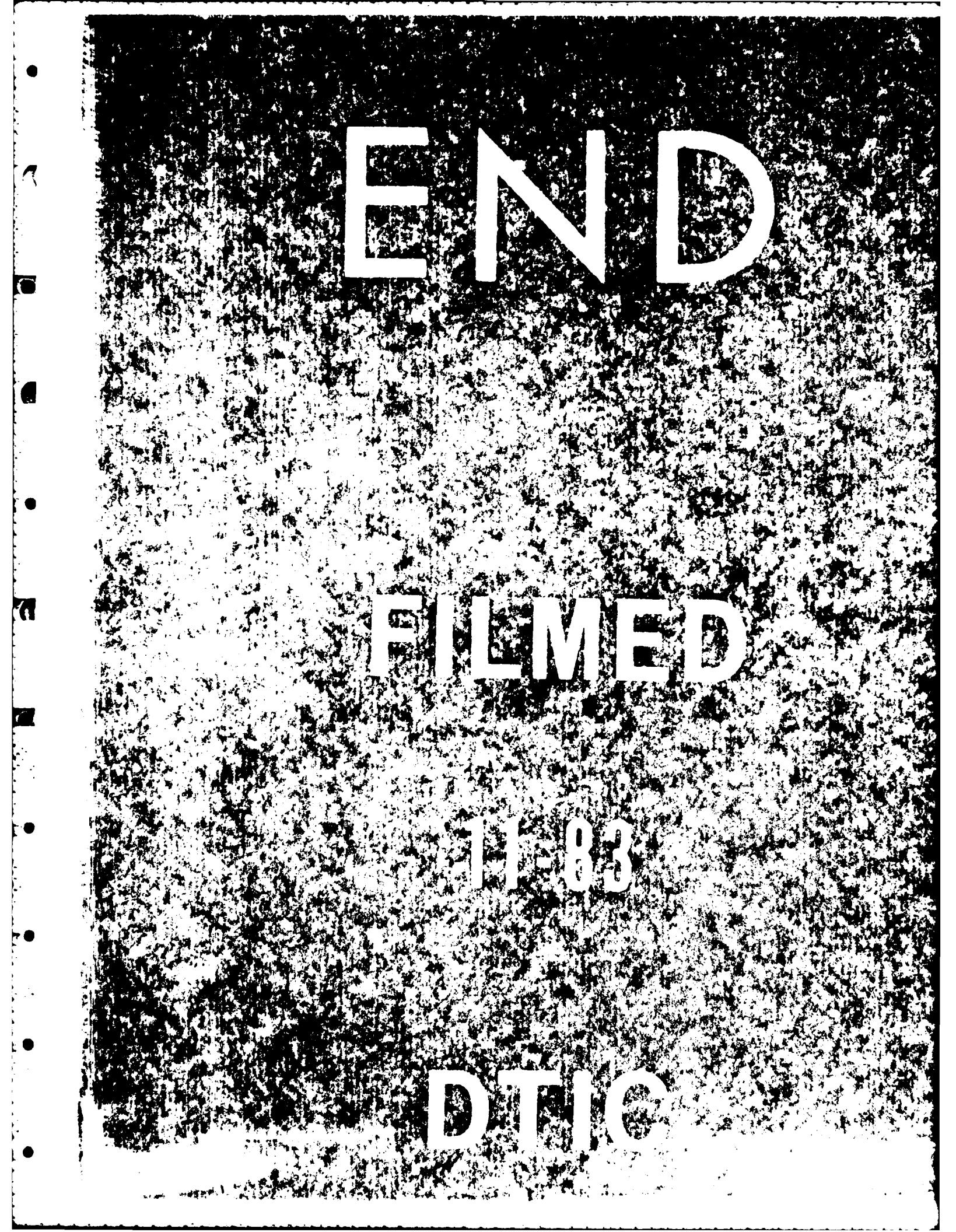
251. Yoshimaru, Hiroshi and Terumi Mukai. "Lack of Experimental Evidence for Frequency-Dependent Selection at the Alcohol Dehydrogenase Locus in Drosophila melanogaster," Proceedings of the National Academy of Science: 876-878, February 1979.

252. Zimm, Bruno. "Theory of 'Melting' of the Helical Form in Double Chains of the DNA Type," The Journal of Chemical Physics: 1349-1356, November 1960.

253. Zimmer, E.A., et al. "Rapid Duplication and Loss of Genes Coding for the Alpha Chains of Hemoglobins," Proceedings of the National Academy of Science: 2158-2162, April 1980.

254. Zukerkandl, Emile. "Some Aspects of Protein Evolution," Biochimie: 1095-1102, 1972.

255. _____, J. Derancourt, and H. Vogel. "Mutational Trends and Random Processes in the Evolution of Informational Macromolecules," Journal of Molecular Biology: 473-490, 1971.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